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REVIEW

New insight into melanin for food packaging and biotechnology applications

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ABSTRACT

Melanin is a dark brown to black biomacromolecule with biologically active multifunctional properties that do not have a precise chemical structure, but its structure mainly depends on the polymerization conditions during the synthesis process. Natural melanin can be isolated from various animal, plant, and microbial sources, while synthetic melanin-like compounds can be synthesized by simple polymerization of dopamine. Melanin is widely used in various areas due to its functional properties such as photosensitivity, light barrier property, free radical scavenging ability, antioxidant activity, etc. It also has an excellent ability to act as a reducing agent and capping agent to synthesize various metal nanoparticles. Melanin nanoparticles (MNP) or melanin-like nanoparticles (MLNP) have the unique potential to act as functional materials to improve nanocomposite films' physical and functional properties. Various food packaging and biomedical applications have been made alone or by mixing melanin or MLNP. In this review, the general aspects of melanin that highlight biological activity, along with a description of MNP and the use as nano-fillers in packaging films as well as reducing and capping agents and biomedical applications, were comprehensively reviewed.

KEYWORDS

Biomedical; functional properties; melanin; nanofillers; nano-melanin; packaging application

1. Introduction

Melanin is a group of heterogeneous functional polymeric materials produced by various organisms, including bacteria, fungi, animals, and plants. In humans, melanins are present in the skin, hair, iris, and in the other parts of the body, including the inner ear, the *subsantia nigra*, and the *locus coeruleus* of the brain (d'Ischia et al. 2013, 2020; Noonan et al. 2012; Solano 2020; Tolleson 2005). It has attracted much attention due to its various physicochemical and biological functions such as photosensitization, photoprotection, metal ion chelation, free radical scavenging, antibiotics, and antioxidant functions (Menter 2016; Meredith and Sarna 2006; Xie et al. 2019). The name "melanin" comes from the ancient Greek *melanos*, meaning "dark," and was first used to call a dark pigment extracted from eye membranes (Solano 2014). The word "melanin" was first used by Berzelius long back in 1840 to refer to the black pigment in animals. Since then, the term has been generally used for black or dark brown organic pigments. It is a dark brown to black biomacromolecules formed by oxidative polymerization of tyrosine (in the case of an animal) or phenolic compounds (in plants and microbes). It is a high molecular weight (318.3 g/mol) blackish-brown pigment produced from oxidation and polymerization of phenolic or indolic compounds (Liu and Simon 2003). Regardless of the source or types, most melanins exhibit some common physical and chemical properties such as high molecular weight, insolubility in water, aqueous acid, and common organic solvents (Meredith and Sarna

2006). Melanin also shows decolorization by oxidizing agents (KMnO₄, NaOCl, and H₂O₂), metal ion chelating ability, and strong UV-vis absorption capability (Meredith and Sarna 2006). Besides, natural and synthetic melanins have a wide range of biochemical activities, including photo-protective, antioxidant, free radical scavenging, and immunomodulatory effects (Solano 2017; Tu et al. 2009). Furthermore, it does not show cytotoxicity, side effects, or antigen responses in cell culture in vitro or in vivo (Araújo et al. 2014; Ju et al. 2016). It has a long lifespan and is very stable since there are no specific melanin-degrading enzymes in living cells. The various functional properties of melanin are shown in Figure 1. Since it has many unique properties as well as the ability to bind to metal ions and some organic compounds like drugs and toxins, it has been widely used in various fields such as optical biomimetics, cosmetics, UV-protective lenses, food colorants, anti-melanoma therapy, and preparation of metallic nanoparticles (Apte, Girme, Bankar, et al. 2013; Ball 2017; Di Mauro, Camaggi, et al. 2019; Dong et al. 2017; El-Naggar and El-Ewasy 2017; Shanmuganathan et al. 2011; Solano 2017; Zhang et al. 2015). Melanin or melanin-like compounds have also been used as coating materials in electronics, sunscreens, energy storage, biofilms, drug delivery systems, and various types of biomedical applications such as theragnostic, phototherapy, bioimaging, biosensors, tissue engineering, photoacoustic imaging, and therapeutic use (d'Ischia et al. 2015; Dario Livio Longo, Stefania, Aime, et al. 2017; Perring et al. 2018; Qi et al. 2019; Solano 2014; Wang, Hou, et al. 2019; Xu

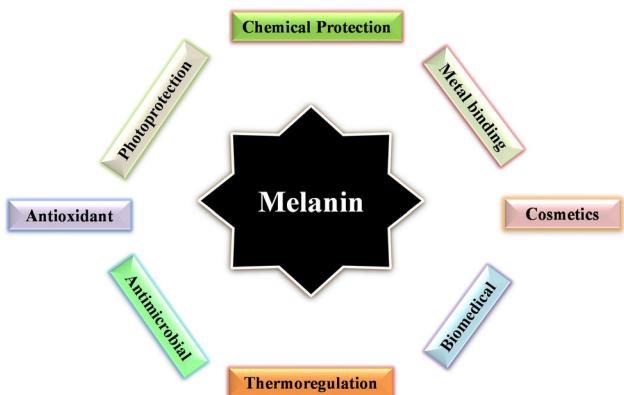


Figure 1. Functional properties of melanin.

et al. 2019; Zhang et al. 2015; Araújo et al. 2014; Lin et al. 2016; Liopo, Su, and Oraevsky 2015; Plonka and Grabacka 2006; Solano 2017, 2020; Wang, Sheng, and Yang 2019). Melanin has also shown a useful role as a reducing and stabilizing agent in synthesizing various nanoparticles (Apte, Girme, Bankar, et al. 2013; Kiran et al. 2014; Roy, Shankar, and Rhim 2019). Melanin nanoparticles (MNP) or melanin-like nanoparticles (MLNP) has also been used for reinforcing or providing functionality to various biopolymer-based films for packaging applications (Łopusiewicz, Jędra, and Mizielińska 2018a; Łopusiewicz et al. 2020; Roy, Kim, et al. 2020; Roy & Rhim, 2019b; Roy, Van Hai, et al. 2020; Wang, Zhang, et al. 2017; Wang et al. 2018; Yang et al. 2020).

This review includes comprehensive information about melanin, such as the source, functional properties, the extraction process, preparation of nano melanin, and various melanin or nano-melanin applications such as capping and reducing agents nanofillers for composite materials, applications in biomedical, food packaging, and cosmetics.

2. Extraction and characterization of melanin

Melanin is a natural pigment extracted from fungi, plants, and animal sources, and the extraction process is mainly source-dependent (Chongkae et al. 2019; Pralea et al. 2019). It is generally bound to a cellular moiety, so the isolation in pure form is challenging. In most cases, melanin was extracted by alkali treatment, followed by melanin purification by acid hydrolysis and washing by centrifugation (Wang and Rhim 2019). For the extraction of melanin from hair, the combined use of acid/base treatment and enzyme extraction process was more efficient than a chemical treatment (Liu et al. 2003). There is a countless process of extraction of melanin from various types of sources. Plant melanin pigment was extracted from tea leaves (Sava et al. 2001) following the process shown in Figure 2.

The authors used a water-soluble grape melanin extraction process to extract melanin from tea leaves (Zherebin et al. 1982). First, the raw materials were washed with boiling water (1:20), then extracted with water at 95 °C for 10 min, and added ammonium hydroxide solution (10%) to the wet tea leaves. The pH was then adjusted to 10.5 and incubated for 36 h, followed by filtration and centrifugation

(15,000 × g for 30 min) to collect the solid product. The extracted solid was acidified by adding HCl solution (2 N), the pH was adjusted to 2.5, incubated at room temperature for 2 h, and then centrifuged at 15,000 × g for 30 min to obtain a crude extract. Next, as a purification step, carbohydrates and proteins were removed using acid hydrolysis, and then lipids were removed by sequentially treating organic solvents such as chloroform, ethyl acetate, and ethanol. Finally, black pigments were obtained using the precipitation method. By applying this extraction process, ~200 mg of melanin-like pigment was obtained from 10 g tea leaves. A similar procedure was used to extract melanin from the seeds of *Osmanthus fragrans* (Wang et al. 2006), as shown in Figure 2. Also, studies of melanin produced by fungi and bacteria have long been known (Jacobson and Tinnell 1993). Many fungal species such as *Aspergillus nidulans*, *Tuber melanosporum*, *Agaricus bisporus*, *Auricularia auricula* (L.), *Hypoxyylon archeri* Berk. etc. and bacterial species such as *Bacillus safensis*, *Actinoalloteichus* sp., *Pseudomonas* sp., *Streptomyces glaucescens*, *Nocardiopsis alba*, etc., have been used to extract melanin-like pigments (Dong and Yao 2012; Tran-Ly et al. 2020). Studies on the extraction of melanin from the fermentation broth of *Ophiocordyceps sinensis*, an entomogenous fungus, have been reported (Dong and Yao 2012; Paim et al. 1990). For the pigment extraction, the culture solution was first acidified with HCl solution (6 M), adjusted the pH to 1.5, and left overnight. Then, the precipitated solid was separated by centrifugation at 15,000 × g for 30 min, washed with 0.01 N HCl solution and distilled water, and finally freeze-dried. After purification, the purified solid matter was dissolved in KOH solution (1 M) and filtered. The collected supernatant was acidified using HCl solution (1 M), and washed the filtered residue with distilled water to obtain black pigment from the fungal source. Various other methods have also been used to separate melanin from different microorganisms depending on the source (Tran-Ly et al. 2020). Bacterial melanin was previously extracted from *Bacillus safensis* using a process similar to fungal melanin. When bacteria were cultured in a nutrient medium, dark pigments were formed (El-Naggar and El-Ewasy 2017; Tarangini and Mishra 2014), then the cells are harvested through centrifugation, followed by acid hydrolysis (HCl treatment, pH 2), and centrifuged the pigment suspension to obtain melanin pellets.

Melanin (naturally isolated or synthesized) is usually insoluble in water, limiting its application (Solano 2014), but is soluble only in alkaline solutions. Methods for characterization and identification of melanin using various techniques are presented in schematic diagrams (Figure 3). For the preliminary characterization of melanin pigments or nano-material forms, UV-vis spectral analysis is useful. The alkaline solution of melanin shows the maximum UV-absorption peak in the range of 200–280 nm, depending on the source (Zonios et al. 2008). The strong UV-light absorption of melanin is mainly due to the structure that scatters and absorbs photons (Hou et al. 2019; Engelen et al. 2012). Synthetic and sepia ink melanins show an absorption peak at 220 nm, then the light absorption continues to decrease at

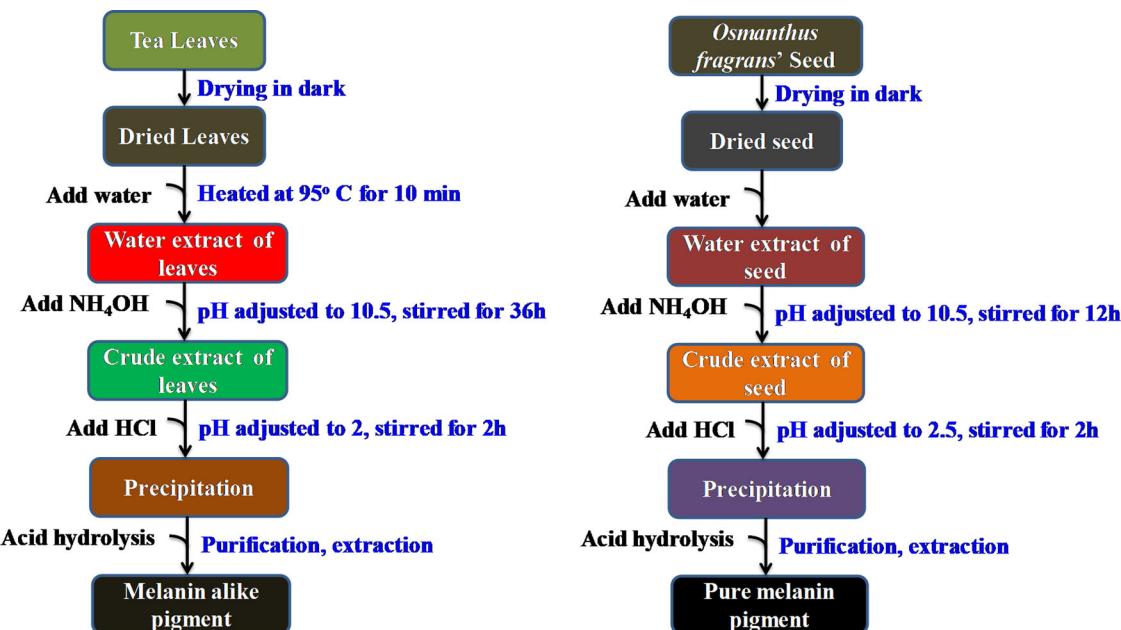


Figure 2. Process of extraction of melanin-like pigment from tea (left) and seed (right).

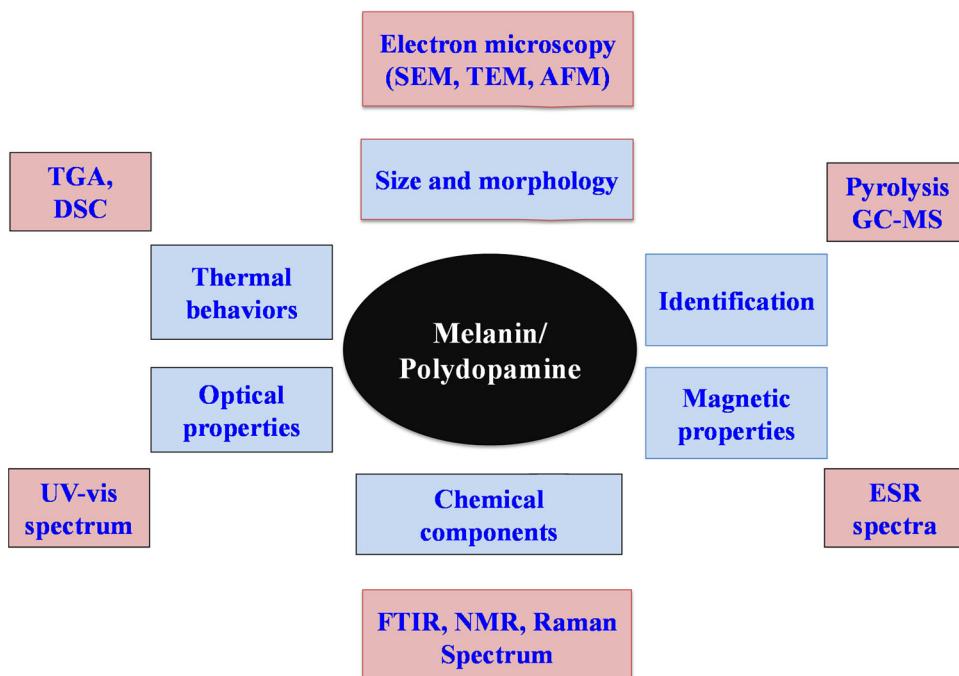


Figure 3. Various techniques for the identification and characterization of melanin or melanin-like pigments.

longer wavelengths (Pralea et al. 2019). FTIR is the most useful and straightforward method to get an idea about the structure of the compound. Depending on the type and source, the IR spectral pattern varies, but many characteristic peaks identify black pigments. Among the various IR bands for melanin such as stretching vibrations of -NH and -OH groups ($3000\text{--}3500\text{ cm}^{-1}$) ascribed to the amine, carboxylic acid, aromatic amines, and phenolic groups of indole, and pyrrole structure of melanin (Selvakumar et al. 2008; Ye et al. 2014; Zou, Zhao, and Hu 2015). Another characteristic band is the bending vibration of N-H, and the stretching vibration of C-N (secondary amine) of an indole ring structure appeared at $1400\text{--}1500\text{ cm}^{-1}$ (El-nagar & El-

Ewasy, 2017). Nuclear magnetic resonance (NMR) analysis is commonly used to obtain more insight and accurate information about melanin's structure. Melanin can be identified using NMR study since it gives chemical shifts at $6\text{--}8\text{ ppm}$ due to the aromatic hydrogens of indole and/or pyrrole ring of the polymeric chain of melanin (Pralea et al. 2019). Both proton and carbon NMR are used for this purpose. Many typical peaks can be found in the proton (^1H) NMR spectra, which confirm melanin's molecular structure (El-Nagar & El-Ewasy, 2017a). The NH group's occurrence connected to indole was observed around $1.3\text{--}2.5\text{ ppm}$ (Ye et al. 2019). In the case of carbon (^{13}C) NMR spectra, the most common peaks are found between $160\text{--}185\text{ ppm}$ due

to the carbon atoms in carboxyl and amide groups or the carbonyl groups of peptide bonds (Pralea et al. 2019). At 120–140 ppm, another significant peak can be found due to the aromatic carbons involved in the indole/pyrrole structures (Xin et al. 2015). Another important tool is the electron spin resonance (ESR) spectrum, which provides information about melanin's magnetic properties (Ju et al. 2011). It has been observed that both natural and synthetic melanin has para-magnetism (Blois, Zahlan, and Maling 1964).

The thermal stability of melanin can be measured using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) analysis. Melanin is thermally stable and usually exhibits multi-step decomposition. The primary thermal decomposition of melanin occurs at very high temperatures ($\sim 900\text{--}1000^\circ\text{C}$) due to the decarboxylation procedure, but the thermal degradation properties depend on the source (Wang and Rhim 2019). It is known that synthetic melanin has higher heat resistance than natural melanin (Simonovic et al. 1990). It also showed excellent stability in food ingredients such as glucose, sucrose, ascorbic acid, and potassium sorbate, which is very useful for applying melanin to food packaging materials. The morphological identification (shape and size) of melanin is usually made by electron microscopy analysis (SEM, AFM, and TEM). SEM is the most used tool to characterize any material's morphology, and AFM and TEM are used for more in-depth studies. According to electron microscopy data, in most cases, the pigment granules are amorphous. They have a spherical or irregular shape with a size range of 30–1000 nm, but melanin's shape and size are highly dependent on the source (Ju et al. 2011; Wang and Rhim 2019).

Commonly used structural analysis methods (UV-vis spectroscopy, IR analysis, NMR) are not suitable for distinguishing different types of melanin pigments. Recently, more facts about melanin structures have been discovered using many advanced techniques like pyrolysis gas chromatography, liquid chromatography-mass spectrometry (LC-MS), various mass spectroscopy (matrix-assisted laser desorption ionization, electrospray ionization, electron impact (EI), fast atom bombardment (FAB), matrix-assisted laser desorption/ionization (MALDI), secondary ion mass spectrometry (SIMS) or laser desorption synchrotron post ionization (synchrotron-LDPI) mass spectrometry) to characterize the synthetic and natural melanin (Latocha et al. 2000) (Pralea et al. 2019). These modern techniques are useful and have been used to confirm the structure of eumelanin and pheomelanin (Liu and Simon 2003). All the tools and characterization methods discussed to identify and characterize melanin are required to judge the pigment's exact analysis. Not all procedures are required to study the extracted black pigment. Basic information can be obtained through solubility and UV-vis spectra. Then various electron microscopy techniques (e.g., SEM, AFM, TEM) with FTIR, NMR, and MALDI can be used for more specific information on the structure and morphology of the pigment. Pyrolysis gas chromatography, LC-MS, and MALDI are sufficient to obtain qualitative evidence. On the other hand, a

direct method of LC-MS analysis after oxidation or hydrolysis of the sample can be used to obtain quantitative data.

3. Sources of melanin

Melanin is found throughout the animal kingdom, except for arachnids, including microorganisms, plants, and animals. In fungi and bacteria, diphenols, the precursor of melanin, are destabilized by enzymatic oxidation to quinones and spontaneously polymerized to form melanin (Borovanský and Riley 2011; El-Naggar and El-Ewasy 2017). Melanin synthesis is regulated by a variety of factors such as genes, ultraviolet rays, and hormones. Sometimes a genetic, hormonal imbalance interferes with pigment synthesis, resulting in little or no coloration in hair, eyes, and skin, leading to albinism (Huang et al. 2017; Nicolaus 2005; Schindler et al., 2019). The chemical structure of melanin is still controversial, but it is highly dependent on polymerization and oxidation conditions during its synthesis, and the final form of melanin depends on the synthesis process or the source of extraction (Liu and Simon 2003). The various precursors and melanin types are shown in Figures 4a–g and 5, respectively.

Most microbial melanin is 1,8-dihydroxyphenylalanine (DOPA) or γ -glutamyl-3,4-dihydroxybenzene (GDHB) based (Figure 4e), but some microorganisms can synthesize melanin from catechol or other phenolic compounds (Eisenman and Casadevall 2012; El-Naggar and El-Ewasy 2017; Langfelder et al. 2003). In plants, melanin is responsible for the coloration of some seeds, berries, and flowers, where they play an essential role in photoprotection (Nicolaus, Piattelli, and Fattorusso 1964). Melanin pigments have been isolated from various sources of plants, including chestnut, sunflower seeds, black beans, black garlic, grapes, and seeds of *Osmanthus fragrans* (Wang et al. 2006; Wang and Rhim 2019). Animal melanin, synthesized from indole or other sulfur-containing compounds (e.g., tyrosine) (Figure 4g), can be found in the skin, hair, feathers, inner ear, pigmented epithelium of uveal tract, adrenal gland, leptomeninges, locust ceruleus, *substantia nigra* of the brain stem, bone, heart, adipose tissue, and pulmonary and digestive tracts (Solano 2014; Francisco Solano 2017; Tolleson 2005; Yerger and Malone 2006). Natural sources of eumelanin include sepiia, human hair pigment, feather melanin, melanosomes, and human neuromelanin (Liu and Simon 2003; Menter 2016). Also, there is melanin precursor-like commercial (L-tyrosine and L-DOPA, dopamine and catecholamines) and noncommercial precursors (DHI, DHICA, and cysteinyl-DOPAs) (Figure 4a–g). Melanin has a macromolecular structure and consists of 5,6-dihydroxy indole (DHI) units and 5,6-dihydroxy indole-2-carboxylic acid (DHICA) groups, where DHI and DHICA are produced from oxidative polymerization of dopamine and cysteinyl-dopamine, respectively (Solano 2014). Black melanin (eumelanin) and red melanin (pheomelanin) are then made via crosslinking reactions.

In higher organisms, melanin present in epidermal keratinocytes, although synthesized in melanocyte cells present at the lower levels of epidermal and dermal cells (Diffey et al. 1995). Melanin pigment is first produced in melanocytes and then transferred to keratinocytes via melanosomes by

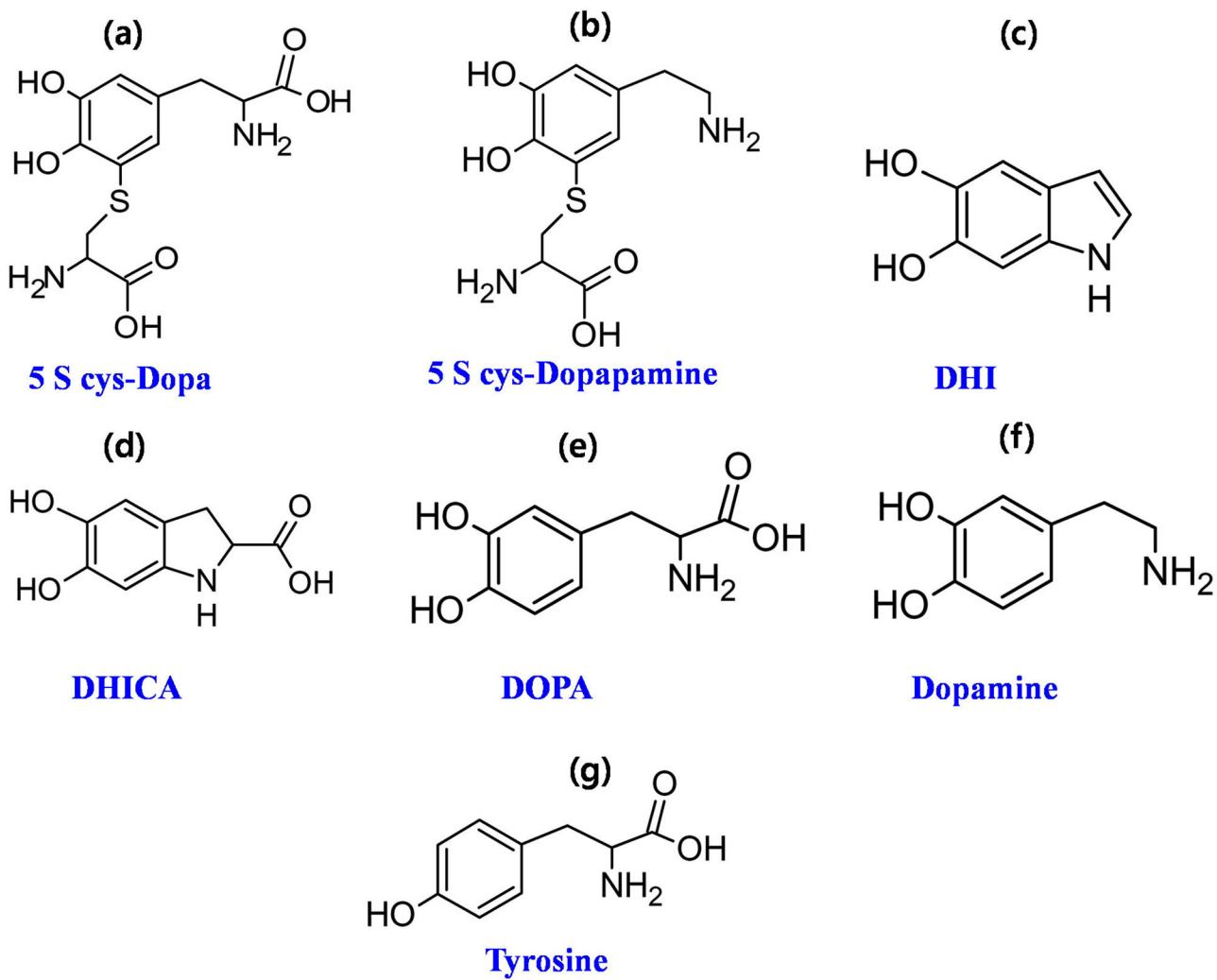


Figure 4. Various precursors for the synthesis of melanin.

supporting melanocyte dendrites (Diffey et al. 1995). As keratinocytes are in close contact with melanin, its synthesis and transport from melanocytes to keratinocytes are performed through a tightly regulated process. In the case of an animal, melanosome is known as the source of synthesis of melanin. This melanosome is also the site of synthesis, storage, and transport of melanin in animals (Marks and Seabra 2001; Raposo and Marks 2007). The pathway of formation of melanosome formation is shown in Figure 6. Melanosomes can be made from two different sources. In the case of smooth endoplasmic reticulum, pre-melanosomes are formed by the coalescence of vesicles and appear to contain parallel filamentous contents, but in the case of rough endoplasmic reticulum and Golgi complex, tyrosinase and other enzymes are synthesized and packaged into vesicles. Subsequently, these fuses with the pre-melanosomes form melanosome, and melanin are finally synthesized from the melanosome.

4. Classification of melanin

Melanin can be primarily classified into three categories based on the source: a) eumelanin, b) pheomelanin, and c) allomelanin (Figure 5). Among them, eumelanin and

pheomelanin are animal-based pigments, and allomelanin is another dark pigment of plants and microorganisms (d'Ischia et al. 2013). Besides the three main types of melanin, there are also neuromelanin, pyomelanin, and synthetic melanins. Melanin pigments are also classified based on their color and solubility properties into brown to black eumelanin and allomelanin, and yellow or reddish-brown sulfur-containing pheomelanin, as well as other types of melanin and synthetic melanins. Characteristics of various types of melanin are shown in Table 1. Eumelanin is black to the brown water-insoluble pigment, mainly found in black hair and sepia ink. Eumelanin is polymers consisting mostly of indole-type units that arise from L-tyrosine or L-DOPA (L-3,4-dihydroxyphenylalanine) oxidation (Figures 4e and g and 5). Pheomelanin is yellow to reddish-brown pigment, soluble in alkaline solution, found in red hair and hen feather melanin (Brumbaugh 1968; Solano 2014). Pheomelanin is derived from the oxidative polymerization of cysteinyl conjugates of DOPA via benzothiazine intermediates (Menter 2016; Meredith and Sarna 2006; Pyo, Ju, and Lee 2016). Both eumelanin and pheomelanin are produced from the same precursor, dopaquinone, formed by tyrosine oxidation via tyrosinase (Menter 2016). The main difference between eumelanin and pheomelanin is the presence or

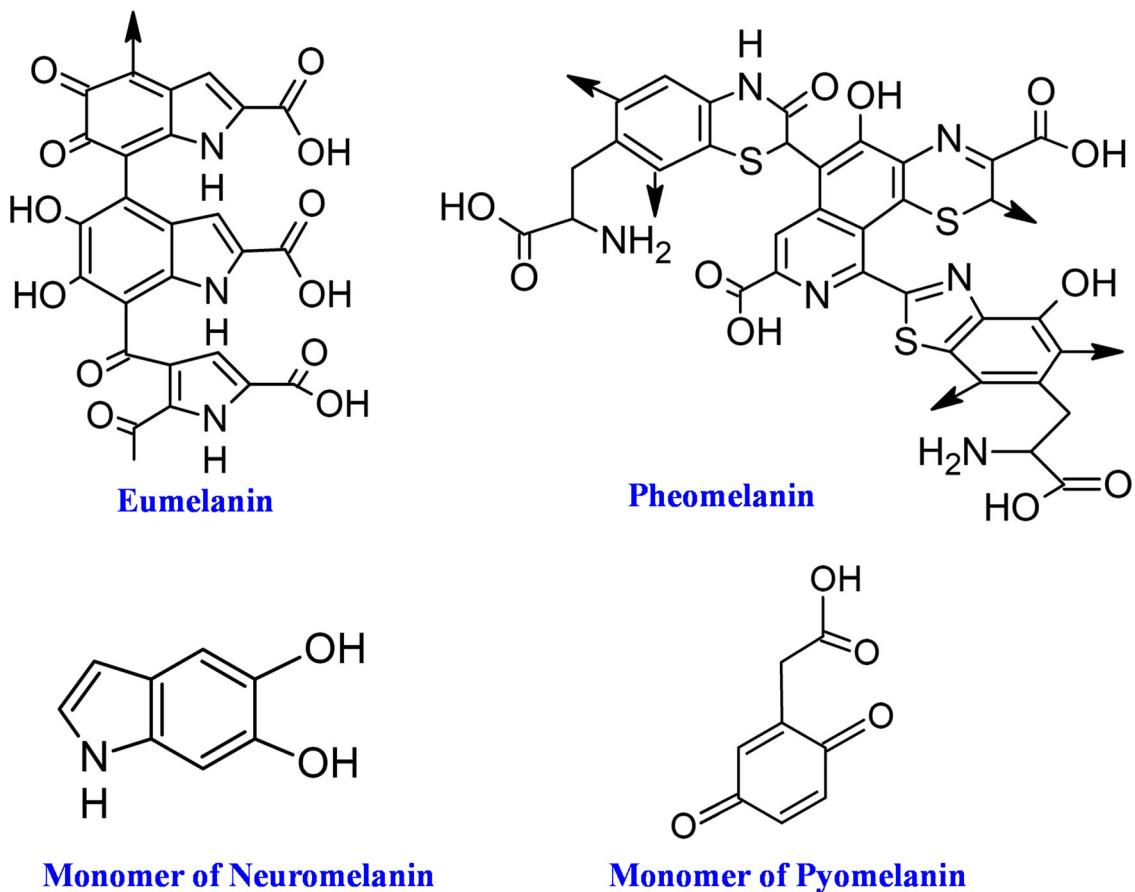
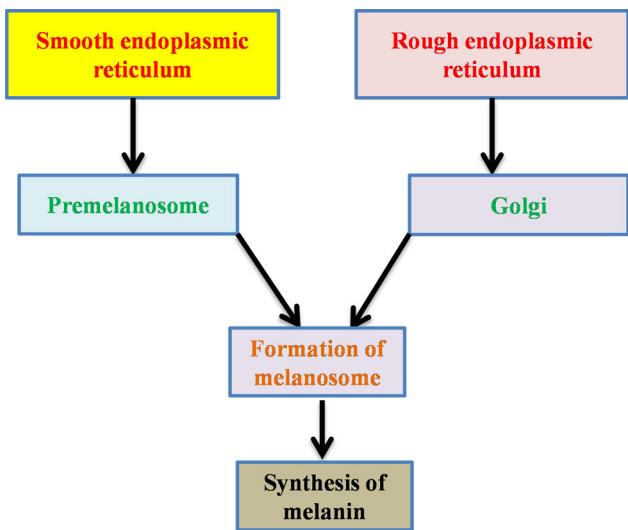


Figure 5. Structure of various types of melanin.



Melanin formation pathway

Figure 6. The schematic synthesis of melanin through melanosome.

absence of sulfur in the melanin component (Yerger and Malone 2006). The source of sulfur is cysteine and glutathione in the phenolic precursors. Eumelanin is found in individuals with dark skin and hair, providing photoprotection. In contrast, pheomelanin is found in individuals with red hair and skin who are more likely to develop skin cancer (Brumbaugh 1968). The synthesis process of eumelanin and

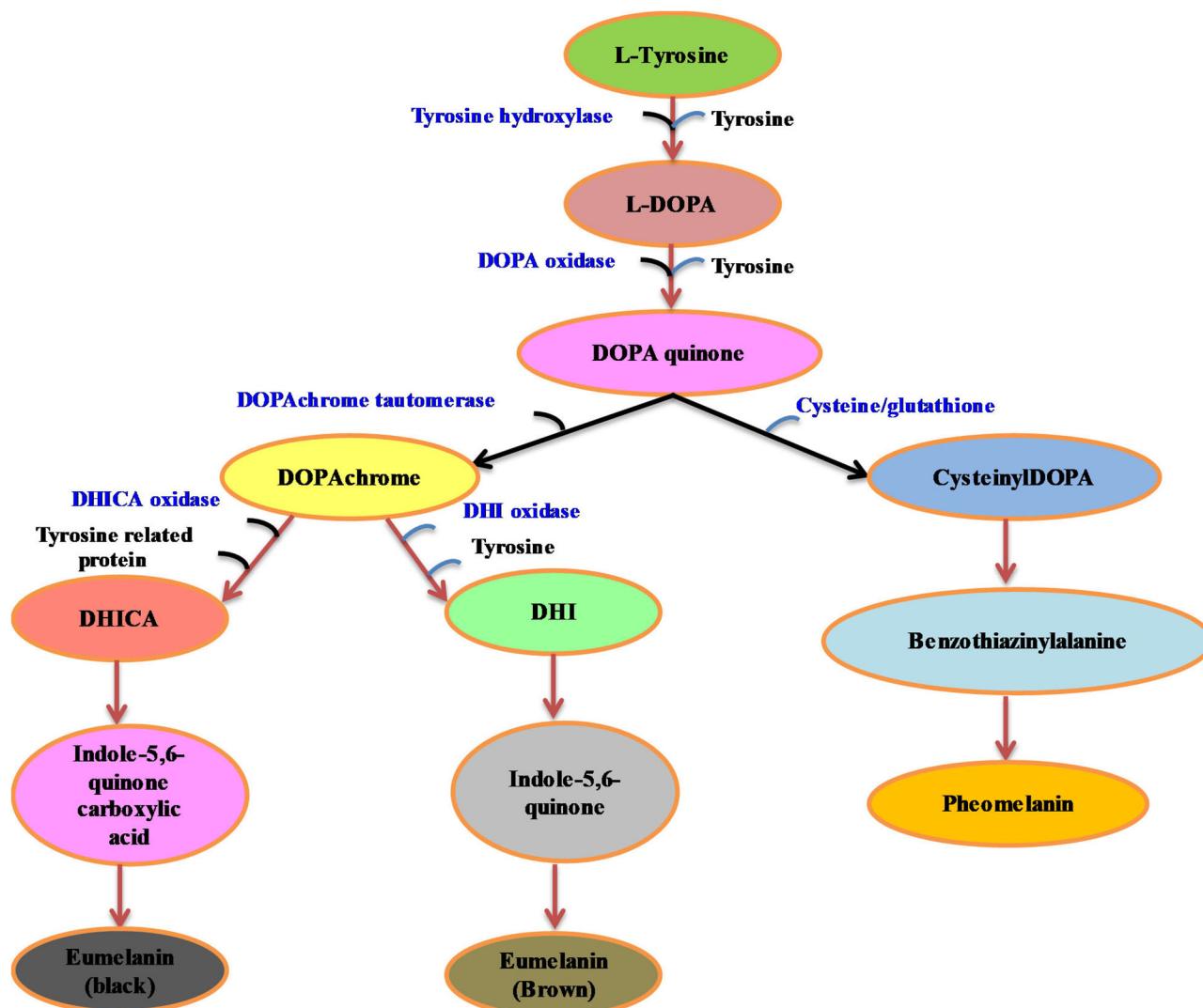
pheomelanin is shown in Figure 7. Allomelanin is a dark non-nitrogen pigment such as plant, fungus, and bacterial melanin. Allomelanin is the least known and highly heterogeneous polymer (Varga et al. 2016). Allomelanins found in the plant kingdom, for example, certain fungi and seeds of some flowering plants, are formed by oxidation of nitrogen-free diphenols such as catechol, 1,8-dihydroxy naphthalene, and γ -glutaminyl-3,4-dihydroxy benzene (Pralea et al. 2019). Synthetic melanin is eumelanin-like pigments formed by chemical oxidation from some diphenolic precursors or by tyrosinase-catalyzed oxidation of L-tyrosine or L-DOPA. The most common synthetic melanin is DOPA-melanin and dopamine-melanin (Ju et al. 2016; Solano 2014).

5. Functional properties

One of the melanin's main functions is to protect cells from UV rays, emit more than 99% of absorbed UV light. It is a stable free radical and can scavenge toxic free radicals (Diffey et al. 1995). In the case of insects, it is used for exoskeletal pigmentation and curing of cuticles. Melanin can strengthen the structure of proteins by crosslinking them. It also provides mechanical strength and can protect proteins from degradation (Meredith and Sarna 2006). The ability to scatter and absorb light is used to shield the photoreceptor, playing a critical role in reptiles' temperature control. The dark color makes it easy to absorb a broad spectrum of visible light, including low quantum energy radiation. Melanin

Table 1. Characteristics of various types of melanin.

Melanin	Characteristics	Occurrence
Eumelanins	Black or brown nitrogenous pigments, insoluble in water and organic solvents, formed by oxidative polymerization of 5,6-dihydroxyindoles derived from tyrosine via DOPA	Animal (hair, feather, fur, skin, scales, choroid, iris, inner ear, etc.)
Pheomelins	Yellow to reddish-brown pigments, alkali-soluble, containing sulfur in addition to nitrogen, formed by oxidative polymerization of cysteine-S-yl-DOPA via 1,4-benzothiazine intermediates	Animal (red hair, freckles, and feathers)
Allomelanins	Brown-to-black, form black spots on leaves and flowers, accumulate in beans and seeds (e.g., <i>Osmanthus fragrans</i>)	Plants, fungi, bacteria
Trichochrome	A variety of sulfur-containing phaeomelanin pigments characterized by a $\Delta^{2,2'}$ -bi(1,4-benzothiazine) chromophore	
Neuromelanin	A complex structure containing both eumelanin and pheomelanin together with other amino acids and oxidation products derived from DOPA	<i>Substantia nigra</i>
Pyromelanin	Brownish melanin derived from homogentisic acid by tyrosinases	
Synthetic melanin	Eumelanin-like pigments, formed by tyrosinase-catalyzed oxidation of L-tyrosine or L-DOPA	

**Figure 7.** Schematic representation of the synthesis of various types of melanin.

also has a metal chelating action because it exhibits stable cationic chelating activity by the anionic function of carboxyl and deprotonated hydroxyl groups. Melanin can resist microbial pathogens as it is formed as part of the immune response to combat the microbial attack in plants, fungi, and invertebrates (Nosanchuk, Stark, and Casadevall 2015). Melanin is also known to have a redox action; in particular, eumelanin exhibits redox properties and generates semi-quinone free radicals by

electron fragmentation between the orthoquinone and catechol parts of the polymer (Menter 2016). Melanin participates in the two-electron redox reactions, and one of the light absorption effects is the photooxidation of the pigment. People with darker skin have more melanin, so they are less likely to develop skin cancer from UV rays because melanin protects the skin from UV rays' harmful effects. Lack of melanin synthesis or absence of pigmentation can also cause albinism.

The biological action of melanin is dependent on the structure and chemical composition (Figures 4 and 5). There are different types of sources and types of melanin pigments, all of which have common physicochemical properties; besides, they have unique features depending on their nature (Table 1). It can generally protect against environmental stress, so it is believed that melanin pigmentation occurred due to the living organism's adaptation to adverse environmental conditions. The properties of melanin, such as antioxidant, optical, electronic, semiconductor, biomedical, and photoprotective actions, are governed by the presence of electrons that are unpaired to the melanin structure (d'Ischia et al. 2015; Solano 2016). It can act as an immune system enhancer and accelerate wound healing and burns (ElObeid et al. 2017). Melanin has anti-inflammatory properties against swelling and irritation (ElObeid et al. 2017). It also acts as an anti-aging agent by reducing free radical production, removing excess free radicals, and increasing the activity of antioxidant enzymes (ElObeid et al. 2017). Besides, melanin can act as a likely material for organic bio-electronic devices such as transistors and batteries (Bernardus Mostert et al. 2012). Both natural and synthetic melanins bind to metals due to melanin's ion-exchange properties (Felix et al. 1978). The redox potential of melanin can protect microorganisms from oxidizing agents such as permanganate, hypochlorite, and hydrogen peroxide (Gidianian and Farmer 2002). It can also be used to protect the eyes by blending with transparent eyeglass lenses to shade short wavelengths.

Among the myriad applications of melanin or melanin-based materials, only antioxidant, photoprotection, UV-light barrier properties, antimicrobial activities, and liver protection were comprehensively discussed.

5.1. Antioxidant

Recently, interest in natural antioxidants has increased due to the side effects of using synthetic chemical antioxidants. Melanin is considered a good candidate for replacing synthetic antioxidants since natural and synthetic melanin has potent antioxidant activity. Melanin molecules have both oxidizing (*o*-quinone) and reducing (*o*-hydroquinone) moieties, present in both eumelanin and pheomelanin, and in turn, quench reactive oxygen or nitrogen species through either electron donation or capture (Borovanský 1996). It is known that the antioxidant action of melanin is attributed to free radical scavenging, peroxide-radical scavenging, and lipid peroxidation activity (Brenner and Hearing 2008). The antioxidant property of melanin has dependent on form and aging (Zou, Zhao, and Hu 2015). The antioxidant properties of melanin or melanin-like pigments are mainly reliant on the oxidation state of the melanin and phenol-quinone structures (Solano 2016). Another possible reason may be melanin's ability to donate or accept electrons, which interact with free radicals through electron transfer processes to neutralize electron radicals (Różanowska et al. 1999). The presence of intramolecular non-covalent electrons is believed to be responsible for antioxidant activity as these electrons

can interact with free radicals and other reactive species (El-Naggar and El-Ewasly 2017).

Melanin isolated from Taihe black bone smooth chicken shows very promising antioxidant activity, which can be useful for the food and pharmaceutical industry (Tu et al. 2009). The antioxidant properties of melanin extracted from Chinese black tea (*Thea sinensis* Linn.) are also well known (Hung et al. 2002). Melanin isolated from sepia ink and black garlic also showed potent antioxidant activity (Wang and Rhim 2019). Kumar et al. (2011) also demonstrated the antioxidant activity of melanin pigment isolated from fungal *Aspergillus* strain. Fungal melanin has excellent antioxidant properties, and melanin obtained from a fungal strain was resistant to hypochlorite and permanganate, and its antioxidant activity has been reported to be similar to those produced by stimulated macrophages (Jacobson, Hove, and Emery 1995). Polydopamine melanin nanoparticles (PDMN) have been reported as a potent antioxidant for protecting free radicals and reactive oxygen species (Qi et al. 2019). The nanoparticles showed excellent free radical scavenging properties (Liu et al. 2013). PDMN has been reported to be a potent antioxidant for the protection of free radicals and reactive oxygen species. The antioxidant property of melanin has dependent on the form and aging of melanin (Zou, Zhao, and Hu 2015). The potent antioxidant activity of melanin is beneficial for food packaging applications. Recently, research interest in bio-based active packaging films is receiving significant interest, and the antioxidant properties of melanin will likely be utilized for this purpose. Previous reports have shown that melanin's antioxidant properties in environmentally friendly packaging films are useful for active packaging applications (Yang et al. 2020; Shankar, Bang, et al. 2019; Wang et al. 2018).

5.2. UV light barrier and photoprotection

The animal kingdom produces melanin primarily to protect against exposure to ultraviolet B (UVB) radiation (Yamaguchi et al. 2006). Ultraviolet A (UVA) can penetrate deeper into the dermis than UVB, so it can be blamed for causing skin photo-aging and skin cancer (Agar et al. 2004; Li et al. 2019). Meanwhile, melanin may act as a photosensitizer after excitation by visible light (Chiarelli-Neto et al. 2011). Today, melanin has attracted attention in cosmetics due to its excellent ability to protect the toxic effects of UV-radiation through light protection (Brenner and Hearing 2008). It has a strong ability to absorb and scatter photons from UV and blue sunlight. Melanin photoprotection may also result from quenching of excited state molecules and scavenging of reactive oxygen species formed in pigment cells (Marrot et al. 1999). Since ancient times, it has been believed that skin pigmentation plays a dominant role in photoprotection. The skin and retina of animals with skin and epidermal tissue contain a large amount of melanin, which is thought to protect against the toxic effects of UV-rays of solar light. Melanosomes in dark skin are not affected by lysosomal enzymes, providing essential functions to protect the skin from UV damage. Melanin not only

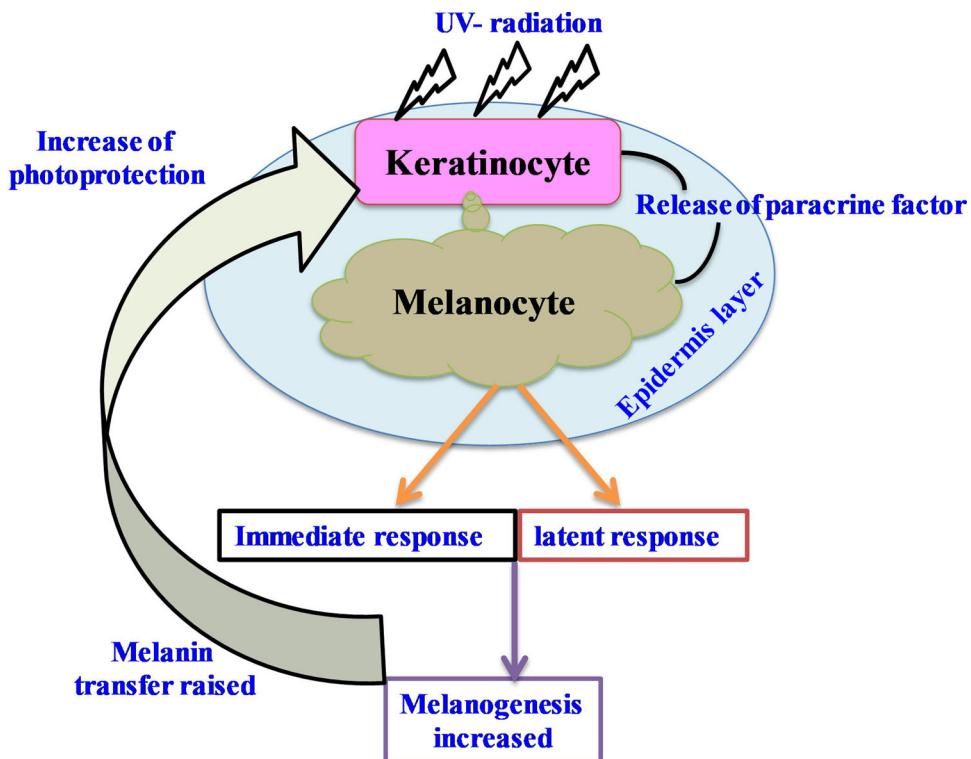


Figure 8. Schematic presentation photoprotection pathway of melanin.

absorbs and scatters UV-light but also has antioxidant and radical scavenging functions (Brenner and Hearing 2008). The UV-light absorbing and scattering properties of eumelanin reduce UV-light penetration through the epidermis of the skin (Kaidbey et al. 1979). It is also clear that dark skin is less susceptible to skin cancer than white skin due to skin pigment's photoprotection (Halder and Bang 1988). It has been reported that dark skin containing melanin has twice the effect of suppressing UV radiation penetration than white skin (Gloster and Neal 2006). PDMN has excellent absorption efficiency in the infrared region and high energy efficiency for heat conversion, and excellent stability for irradiation; therefore, PDMN can be used as an excellent photothermal protection material (Liu et al. 2013).

Recently, as the destruction of the ozone layer progresses, the incidence of skin cancer caused by UV is increasing. In this context, PDMN may act as an excellent agent for controlling such skin damage. There is also evidence of the damaging effects of melanin after exposure to UV radiation (Kvam and Dahle 2004). Melanin can react with DNA, acts as a photosensitizer, synthesizes free radical species after UVA radiation exposure, and causes single-strand breaks in DNA (Marrot et al. 1999). The photoprotection pathway of melanin is shown schematically in Figure 8. UV radiation can induce the pigment synthesis by increasing melanin production in melanocytes. It has been found that paracrine factors like adrenal stimulating hormone required for fibroblast growth factor and endothelin-1 increase when the skin comes in contact with UV (Kobayashi et al. 1998). UV radiation can also induce the activation of transcription factors (Abdel-Malek, Kadekaro, and Swope 2010). The increased paracrine factor plays an important role in activating melanocytes and shows an

immediate and late response. As a result, this complex process increases melanogenesis, transports melanin to the keratinocytes of the epidermal layer, showing photoprotection against UV radiation (Moreiras et al. 2019). Therefore, blending melanin into a food packaging film or coated paper can block UV and visible lights from food. Melanin-added packaging film with high UV protection can be used for active packaging applications, preventing photodegradation to maintain the quality of the packaged food and increase the shelf life. The reason for melanin's UV protection is that it can quickly convert photon energy from UV light into heat to prevent destructive photodegradation (Forest and Simon 1998). Previously, it was reported that the UV shielding performance of poly(vinyl alcohol) films prepared by adding melanin was similar to those prepared by adding other inorganic UV absorbers (Wang, Li, Ma, et al. 2016; Wang, Zhou, and Wu 2014), which indicates that melanin is suitable for the manufacture of UV protective packaging films. Many other reports have also shown that melanin can be added to various polymer-based films to make UV-blocking packaging films (Łopusiewicz, Jędra, and Mizielińska 2018a; Łopusiewicz et al. 2020; Shankar, Wang, et al. 2019; Roy and Rhim 2019d; Roy, Kim, et al. 2020; Roy, Van Hai, et al. 2020). Recently, Bang, Shankar, and Rhim (2020) prepared a UV-blocking packaging film by adding melanin into polypropylene/poly(butylene adipate-co-terephthalate) composite films and demonstrated its anti-greening effect on potatoes.

5.3. Antimicrobial activity

The antimicrobial activity of melanin is also an important aspect to explore. Several reports have already shown the

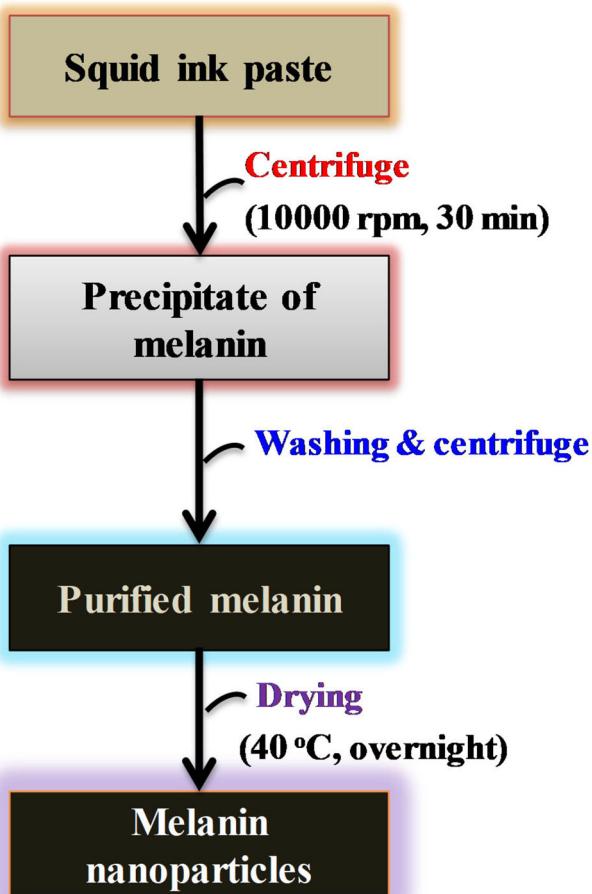


Figure 9. Procedure for the preparation of melanin nanoparticles isolated from sepiia ink.

antibacterial activity of melanin pigments. Recently, Xu et al. (2017) studied the antibacterial activity of melanin isolated from *Lachnum YM30* against *Vibrio parahaemolyticus* and *Staphylococcus aureus*. They reported that the antimicrobial activity was primarily due to membrane damage, increased leakage of cell contents, and decreased cell membrane potential. Laxmi et al. (2016) found that *Providencia rettgeri* isolated melanin could inhibit the growth of *P. aeruginosa*. In another report, it has been shown that the *A. auricula* melanin inhibited biofilm formation of *E. coli*, *P. aeruginosa*, and *P. fluorescens* (Bin et al. 2012). Kuang, Guo, and Messersmith (2014) reported the antibacterial activity of DOPA-melanin coatings against *S. aureus*. Zhao et al. (2007) reported on synthetic melanin's broad antimicrobial activity, and they observed that bacterial cells aggregated and lost cell mobility by the pigment. Fukuda and Sasaki (1990) found that some drugs' antibacterial activity changed after binding to melanin. Melanin is also known to protect microbes from host defenses, and the same is applied to antimicrobial therapy by combining with antibacterial and antifungal agents (Nosanchuk and Casadevall 2006). Melanin isolated from *Pseudomonas balearica* exhibited potent antibacterial activity against phytopathogenic strains (*Erwinia chrysanthemi* 3937VIII and *Erwinia carotovora* 197 strP), foodborne pathogenic bacteria (*Staphylococcus aureus* and *Escherichia coli* TG1), and yeast (*Candida albicans*)

(Zerrad et al. 2014). Vasantha Bharathi, Lakshminarayanan, and Jayalakshmi (2011) reported that melanin synthesized from actinomycetes showed antimicrobial activities against *E. coli*. Composite of melanin and poly(hydroxybutyrate) nanocrystals have been reported to exhibit potent antibiofilm activity against foodborne pathogenic bacteria (Kiran et al. 2017). Recently, antibacterial properties of melanin and nanoparticle (TiO_2) hybrid materials have been reported (Vitiello et al. 2017). It has been reported that soluble melanin synthesized using dopamine, norepinephrine, and serotonin showed excellent anti-HIV-1 activity (Montefiori et al. 1990). A possible reason for the antiviral action is the interaction of viral proteins with melanin. There are also reports of anti-HIV activity of L-DOPA melanin in cell lines (Montefiori and Zhou 1991). They showed that melanin has excellent anti-HIV activity by inhibiting gpl20-CD4 binding. Synthetic melanin also showed inhibition of HIV-1 without cytotoxicity at low doses (Sidibe et al. 1996). Therefore, melanin can be applied as a promising material as an antibacterial agent used in biomedical and engineering fields. Antibacterial packaging films with added melanin have also been reported recently (Kiran et al. 2017; Łopusiewicz, Jędra, and Mizielińska 2018a; Roy and Rhim 2019d). Kiran et al. (2017) showed that a polyhydroxybutyrate-based film added with nanomelanin produced by a *Pseudomonas* sp. could form biofilm against multi-drug resistant *S. aureus*. In another report, Łopusiewicz, Jędra, and Mizielińska (2018a) described the use of melanin extracted from *A. bisporus* in food packaging application. They made PLA-based film and found that the melanin-added PLA film showed potent antibacterial activity against *E. faecalis*, *P. aeruginosa*, and *P. putida* but no effective activity against *E. coli* and *S. aureus*. The difference in antimicrobial activity may be due to different molecular structure, composition, and particle size. Roy and Rhim (2019d) also recently tested the antibacterial activity of carrageenan-based films incorporated with melanin isolated from sepiia ink against foodborne pathogenic bacteria, *E. coli* and *L. monocytogenes*. They found the antibacterial activity was dependent on the melanin concentration and showed stronger antibacterial against *E. coli* than *L. monocytogenes*. In addition, there is a report of practical applications of melanin as a food additive to prevent rancidity due to the presence of bacteria (Zhu, He, and Chu 2011). In this report, melanin can protect food from foodborne pathogens, although its antimicrobial activity varies greatly depending on the source and type of melanin.

5.4. Liver protection

Melanin-like pigments also showed an important activity that favors liver protection. The protective activity of melanin in liver function was observed for the carcinogen hydrazine. The liver's protective function was measured using the antioxidant properties of the melanin-like pigment derived from black tea, and it was found that the pigment can protect the liver from damage caused by hydrazine (Sava et al. 2003). Hung et al. (2003) also shown that tea

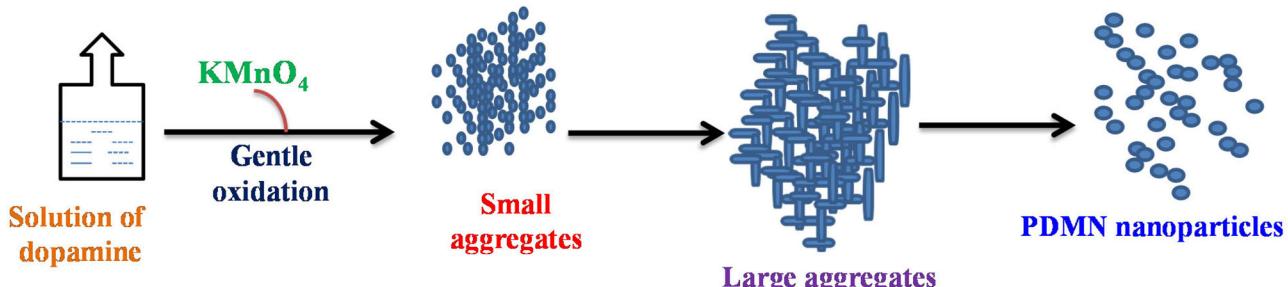


Figure 10. Process for the simple chemical synthesis of dopamine-mediated PDMN nanoparticles.

melanin can protect the liver from hydrazine-mediated oxidative toxicity.

6. Nano-melanin

Recently, studies on melanin or melanin-like compounds have attracted considerable attention due to the versatility of melanin application (Caldas et al. 2020). In particular, natural or synthetic nano-structured melanin has been used in food packaging and biomedical applications. Wang and Rhim (2019) isolated melanin from black garlic and sepia ink and suggested their potential use in food additive, food packaging, and biomedical applications. They isolated MNP with a diameter of 100–200 nm using the process shown in Figure 9. PD is sometimes considered eumelanin because of its structural and structural similarities (Barclay et al. 2017; d'Ischia et al. 2015; Yanlan Liu, Ai, and Lu 2014; Zhong et al. 2019). Kim, Ju, and Lee (2012) produced the water-soluble MLNP with a spherical form by oxidative polymerization of 3,4-dihydroxyphenylalanine (DOPA) with $KMnO_4$ following the process shown in Figure 10. The synthesized MNP exhibited properties similar to known natural and synthetic melanin, and the synthesized MLNP showed properties identical to the black color of melanin (eumelanin), displaying the maximum light absorption at 212 nm. FTIR spectrum data also provides structural information on MNP/MLNP. Microscopic techniques such as SEM, TEM, and AFM have been used to test the morphology of MNP/MLNP. Melanin-like nanoparticles were prepared using dopamine hydrochloride and sodium hydroxide, followed by spontaneous oxidation to generate MLNPs (Ju et al. 2011). Dong et al. (2014) also prepared melanin-like pigment following the process shown in Figure 11a. The biosynthetic and synthetic routes of eumelanin and PD are shown in Figure 11b. For the biosynthesis of natural eumelanin, the starting molecule is tyrosine/DOPA, converted to DOPAquinone and DOPAchromium via tyrosinase-catalyzed reactions. The DOPAchromium is decomposed into DHI or DHICA by tyrosinase-related protein 2 (Tyrp2), and then oxidative polymerization reaction of DHI/DHICA produces eumelanin pigment (d'Ischia et al. 2014).

Surface modification of the synthesized MNP can be performed using thiol-terminal methoxy-poly(ethylene glycol), and the modified melanin particles can be used for additional functional conjugation. It has been reported that chemically synthesized melanin can bind to heavy metals from aqueous media, and Pb, Cu, and Cd ions have an

excellent binding affinity for MLNPs (Kim, Ju, and Lee 2012). Therefore, it is possible to take advantage of MLNP's ability to bind metals for contaminated wastewater bioremediation. Besides, the chemically generated MLNP has excellent photoacoustic efficiency, and this has been applied to photoacoustic tomography as a new contrast agent, which proved to be very promising for biomedical imaging (Liopo, Su, and Oraevsky 2015). Recently, Huang et al. (2017) showed that MLNP could act to some extent as an artificial melanosome. They synthesized MLNP using spontaneous oxidation of dopamine, and the nanoparticles have been endocytosed, which undergo perinuclear aggregation resulting in a microparasol in human epidermal keratinocytes. These synthetic analogs mimic the properties of natural melanosomes. Melanin-coated silica nanoparticles were also synthesized using the enzymatic polymerization of 3,4-dihydroxyphenylalanine and/or 5-S-cysteinyl-3,4-dihydroxyphenylalanine on the surface of silica nanoparticles (Schweitzer et al. 2010). The melanin-coated nanoparticles were used to protect the bone marrow when cancer cells were treated with radiation therapy (Schweitzer et al. 2010). The chemically synthesized, water-soluble MLNPs were used as an effective nano-drug in iron overload therapy for living animal model systems (Yan et al. 2016). Methoxy polyethylene glycol amine-functionalized melanin has also been used as a proficient drug-delivery system for imaging chemotherapy (Zhang, Zhao, et al. 2017). Recently, Chu et al. (2016) also suggested that MNPs isolated from *Sesamum indicum* L. have outstanding cancer photothermal therapy activity and are beneficial for mapping sentinel lymph nodes. Nano-melanin has also been extracted from sepia ink using a simple centrifugation process (Wang, Li, Wang, et al. 2016). They produced monodisperse spherical nano-melanin from sepia inks with a size range of 100–200 nm using a simple dilution and repeated centrifugation (Figure 12) (Roy and Rhim 2019b; Roy, Shankar, and Rhim 2019; Wang and Rhim 2019; Wang, Li, Wang et al. 2016).

7. Application of melanin/nano-melanin

7.1. Reducing and capping agent

Recently, there is a growing interest in the green synthesis of metallic or metallic oxide nanoparticles using biomaterials such as plant extracts, biopolymers, and microorganisms. Melanin can also be used to reduce metal ions for the production of metal nanoparticles. It can act as a reducing

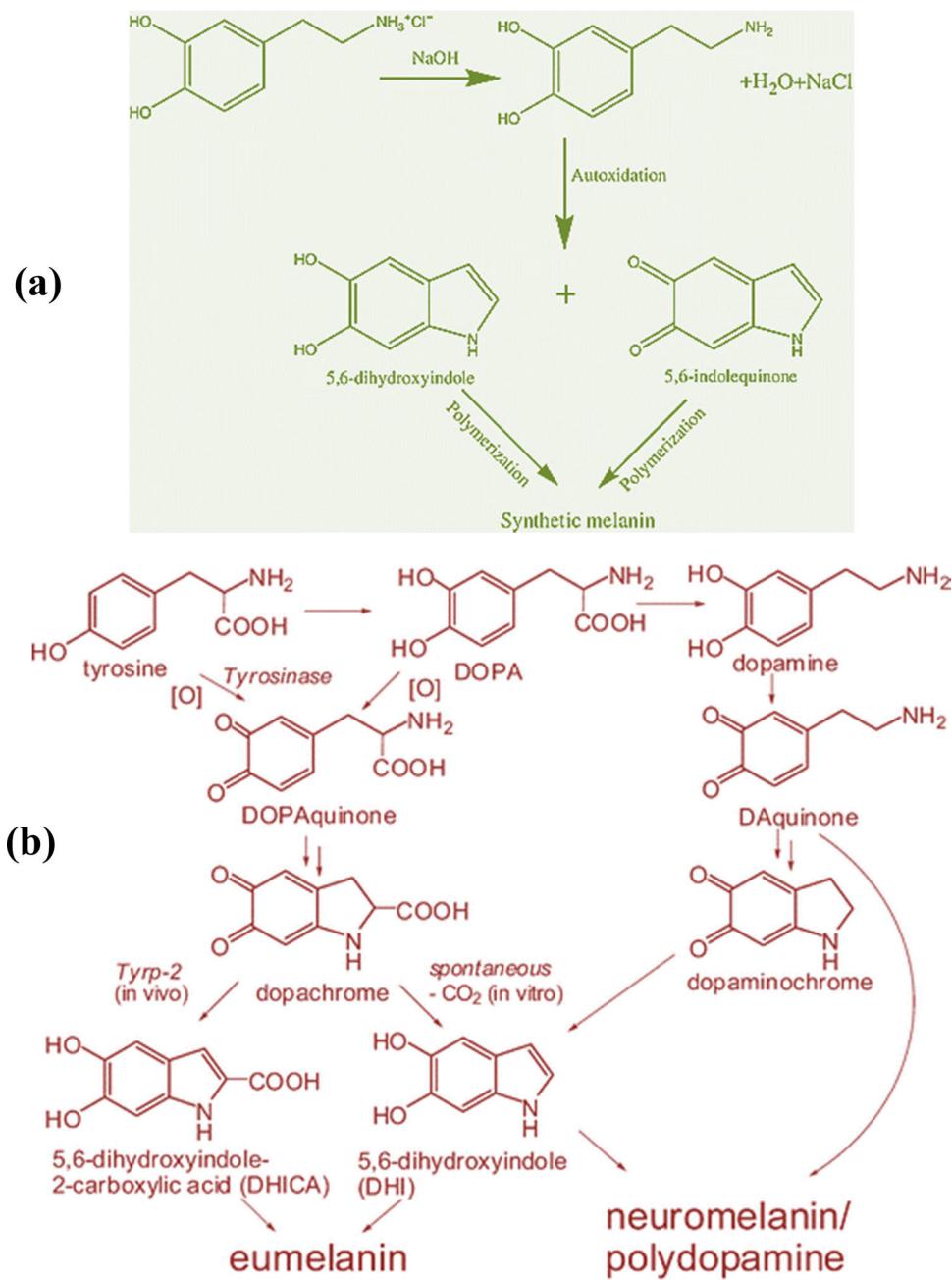


Figure 11. (a) Process for the preparation of synthetic melanin (Dong et al. 2014). (b) Biosynthetic and synthetic pathways for forming eumelanin and PD (d'Ischia et al. 2014).

agent and stabilizer to synthesize metal nanoparticles, so no additional chemicals are needed to reduce or stabilize the nanoparticles. The role of melanin in the synthesis of metallic nanoparticles (silver and gold) is shown schematically in Figure 13. The addition of metal salt (e.g., silver nitrate or auric chloride) to the melanin solution with shaking and agitation for a prescribed time produces melanin-mediated nanoparticles. The process is simple and can be easily scaled-up for large-scale production. There are many reports on the synthesis of metal (silver, gold) or metal oxide (CuO , ZnO) nanoparticles using melanin as a greener reducing agent (Table 2).

Apte, Sambre, et al. (2013) reported the synthesis of silver nanoparticles (AgNP) using cell associate melanin. They extracted melanin from the marine strain *Yarrowia lipolytica*

NCYC 789 and used the cell-associated melanin to reduce silver nitrate to synthesize monodisperse AgNP with an average of 15 nm. The synthesized nanoparticles were very effective in preventing bacterial growth and the formation of biofilm. In another report, the same group showed that *Yarrowia lipolytica* NCIM 3590 cells in the presence of L-DOPA/L-tyrosine could produce more melanin pigment in the growth medium (Apte, Girme, Bankar, et al. 2013). They have used microbial melanin for the synthesis of silver and gold nanoparticles. The average size of the AgNP and AuNP was 7 nm and 20 nm, respectively. Synthesized nanoparticles were tested for antifungal action and applied as a paint additive, giving an excellent effect. The mechanistic action of DOPA for the synthesis of metal nanoparticles is schematically shown in Figure 14. During the conversion of

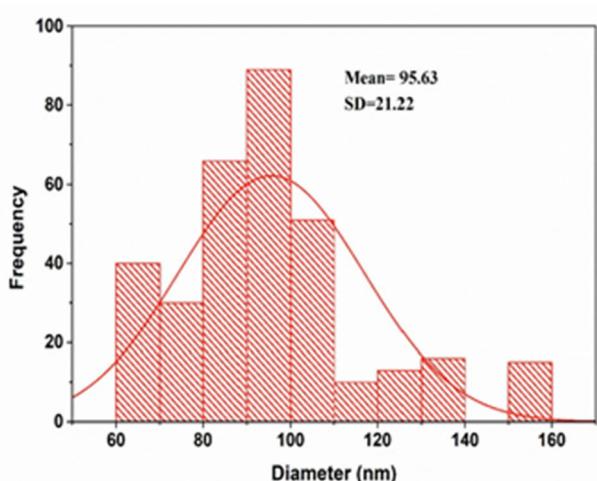
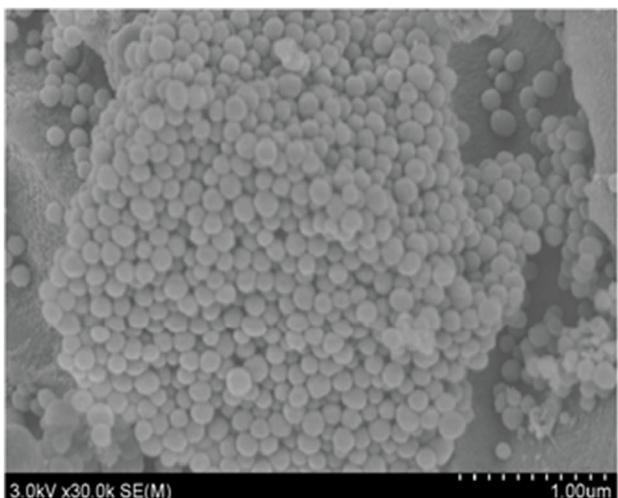


Figure 12. Melanin nanoparticles isolated from squid ink (Roy and Rhim 2019b).

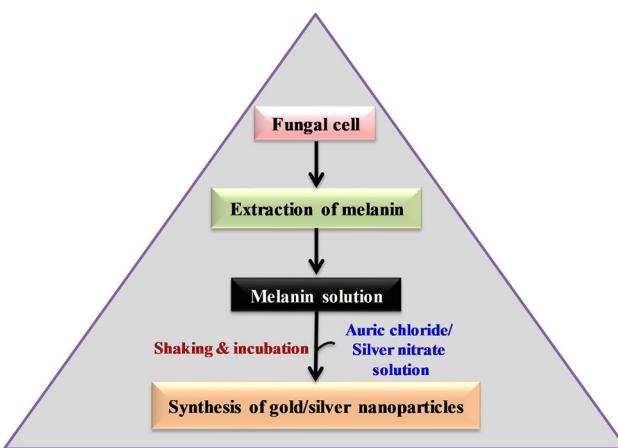


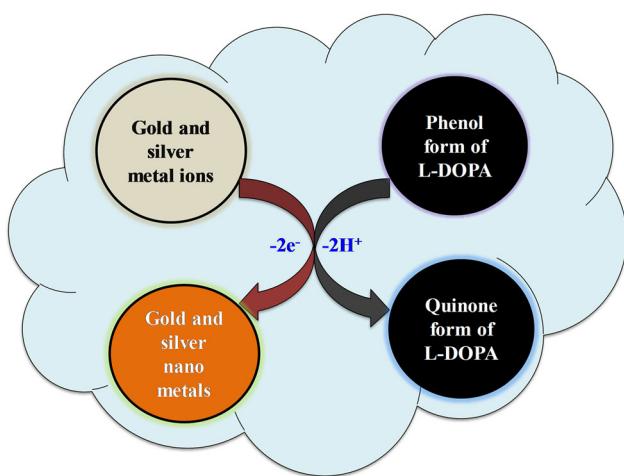
Figure 13. The function of melanin as a reducing and stabilizing agent for the synthesis of nanoparticles.

hydroxyl moiety to quinone moiety of DOPA, two reducing equivalent hydrogen ions are produced, converting the metal ions into elemental nanomaterials. Apte, Girme, Nair, et al. (2013) also reported on the biosynthesis of melanin-mediated AuNPs using the same strain *Yarrowia lipolytica*. They synthesized melanin-mediated AuNPs using two different methods in the presence of melanin extracted from cells and

L-DOPA as an inducer. The produced AuNPs were spherical, and they were found to be a very useful antibiofilm agent. Madhusudhan, Agsar, and Sulochana (2015) also reported on the melanin-based biocompatible synthesis of AgNP. They prepared AgNPs using microwave radiation with water-soluble melanin synthesized by *Streptomyces lusitanus* DMZ3. The obtained nanoparticles had a size range of 13 to 22 nm and showed excellent antioxidant activity. The authors also tested the cytotoxic effects of melanin-mediated AgNPs on saltwater shrimp and showed that biocompatible AgNP could act as a potential cytotoxic agent. Kiran et al. (2014) also synthesized AgNPs using melanin isolated from actinobacterium *Nocardiopsis alba* MSA10. The formed AgNPs had a uniform and stable nanostructure in the size range of 20–50 nm and exhibited a wide range of antibacterial activity against food-borne pathogens. El-Batal et al. (2017) synthesized copper oxide nanoparticles using melanin isolated from *Streptomyces cyaneus* strain. Copper oxide nanoparticles were synthesized using radiolytic action in the presence of copper salt and melanin as a reducing and stabilizing agent. The nanoparticles obtained were essentially monodisperse to a size of about 30 nm. They applied nanoparticles to food-borne pathogens, and the results proved to be very useful in the application of food packaging materials. El-Batal and Al Tamie (2016) also produced AgNP using melanin extracted from *Aspergillus oryzae*. The nanoparticles obtained were spherical and had a size range of 7.52 nm to 36.0 nm. They also found the AgNP had a wide range of intense antimicrobial activity against various bacterial and fungal strains. Dong et al. (2017) also reported the synthesis of melanin template surface-enhanced Raman scattering (SERS) active AgNP applications in intracellular melanogenesis. They synthesized AgNP using synthetic alcohol-soluble melanin and silver-ammonia complex. The average size of the obtained nanoparticles was about 200 nm, which was a rather large particle. The synthesized nanoparticles were used for imaging using the SERS method, and the observed results were promising to study the biological action of melanin. Recently, Roy, Shankar, and Rhim (2019) also found that melanin isolated from sepio ink has excellent AgNP production potential. The size distribution of the synthesized AgNP was skew-symmetrical, with the size range of 10–50 nm. They used the AgNP for the preparation of bio-polymer-based nanocomposite film for active packaging applications. Roy and Rhim (2019a, 2019c) also used the melanin for stabilizing CuO and ZnO nanoparticles to prevent forming aggregation during their preparation. They found that the presence of melanin greatly influenced the shape, structure and properties of the nanoparticles. Gurme et al. (2019) also tested the synthesis of AgNP using melanin isolated from bacteria *Aeromonas* sp., and they found that the optimum condition for the production of AgNP was 14.12 h in 2.62 mM AgNO₃ at a melanin concentration of 32.30 μg/mL at 54.86 °C. The AgNP formed was spherical and ranged in size from 20 to 50 nm, and the melanin mediated AgNP exhibited potent antioxidant and antimicrobial activity. Therefore, melanin can be used for the eco-friendly production of metal nanoparticles by acting as a reducing

Table 2. Synthesis of various nanoparticles using melanin.

Nanoparticles	Description	References
Ag	The synthesized nanoparticles were monodispersed with an average size of about 15 nm	Apte, Sambre, et al. 2013
Au	The synthesized nanoparticles were spherical shaped.	Apte, Girme, Nair, et al. 2013
Ag and Au	The obtained eco-friendly AgNP have an average size of 7 nm, and AuNP have an average size of 20 nm	Apte, Girme, Bankar, et al. 2013
Ag	The obtained nanoparticles have size ranges of 13–22 nm and showed excellent antioxidant activity	Madhusudhan, Aagsar, and Sulochana 2015
Ag	The formed AgNP gave uniform and stable nanostructures in size range of 20–50 nm	Kiran et al. 2014
CuO	The obtained nanoparticles were monodispersed and size of 30 nm	El-Batal et al. 2017
Ag	The obtained nanoparticles have size ranges of 7.52 nm to 36.0 nm and spherical	El-Batal and Al Tamie 2016
SERS active Ag	The obtained average sizes of the nanoparticles were on the higher side ~200 nm	Dong et al. 2017
Ag	The formed nanoparticles have a size range of 20 to 40 nm and a spherical shape	Gurme et al. 2019
Ag	The formed nanoparticles were skewed-symmetrical and in size range of 10–50 nm	Roy, Shankar, and Rhim 2019
ZnO	Melanin capped ZnO NP was flake shaped and had a size range of 80–260 nm	Roy and Rhim 2019c
CuO	Melanin stabilized CuO NP was roughly spherical and in the 20–130 size range.	Roy and Rhim 2019a

**Figure 14.** Mechanistic aspects of biosynthesis of metal nanoparticles by L-DOPA induced melanin.

agent for metal ions and a capping agent for preventing aggregation of the nanoparticles.

7.2. Nanofillers

Melanin or melanin-like compounds were used as nanofillers for the production of new composite materials because these pigments allow strong adhesion and reactivity with ions (Ball 2017; Ball et al. 2012; Caldas et al. 2020; Lyngé et al. 2011; Maher, Mahmoud, Rizk, & Kalil, 2019; Roy, Shankar, and Rhim 2019; Wang, Li, Ma, et al. 2016). Wang et al. (2015) prepared a nanocomposite by mixing MLNPs with poly(vinyl alcohol) (PVA) and found that melanin acts as a reinforcing agent with improved the mechanical properties of PVA even with the addition of small amounts of melanin. The melanin-added polyurethane composite films showed excellent mechanical properties (Wang, Li, Wang, et al. 2016). The addition of melanin also improved the thermal stability of the PVA-based composite film (Dong et al. 2014). Wang, Su et al. (2017) reported that the PVA-based nanocomposite film incorporated with bioinspired dopamine-MNPs showed excellent UV-shielding property. They also found that hollow nanoparticles are more efficient UV light absorbers compared to ordinary nanoparticles. Recently, Roy and Rhim (2019b, 2019d) prepared agar and carrageenan-based nanocomposite films by reinforcing them

with MNP and found that the incorporation of MNP improved not only physical properties (UV-shielding, water vapor barrier, mechanical, and hydrophobicity) but also functional properties (antioxidant and antimicrobial) of the film. Shankar, Wang, et al. (2019) prepared gelatin-based nanocomposite film using MNP as nanofillers, and they also found the addition of MNP significantly improved mechanical, UV-shielding, water vapor barrier properties, and antioxidant properties of the film. Besides, melanin was used to increase the biocompatibility of metal nanoparticles. The biocompatibility of Fe_3O_4 nanoparticles coated with PD was significantly increased compared to the uncoated counterpart (Si and Yang 2011). Also, the deposition of melanin- Fe_3O_4 composite films on gold electrodes helped catalyze hydrogen peroxide (Orive et al., 2007). There is also a report on PD-capped magnetic nano chains for functionalization with thiol-modified polyethylene glycol (Zhou et al. 2015). Chen et al. (2015) reported that the deposition of thin PD film on AuNP synthesized by citrate capping showed steady surface plasmon resonance. It has also been observed that PD is used to decorate multi-walled carbon nanotubes, which ultimately act as a membrane fuel cell in conjugation with nanoparticles (Long et al. 2016). Thus, melanin or melanin-like compounds are promising nanofiller materials for making functional composite materials, and the composite materials have high potential in biomedical and food packaging applications.

7.3. Biomedical applications

Melanin or melanin-based nanoparticles have been widely used in biomedical applications (Caldas et al. 2020; Fan et al. 2019; Jiang et al. 2019; Longo, Stefania, Callari, et al. 2017; Qi et al. 2019), as shown in Figure 15. Several review articles on the biomedical applications of melanin or MLNP are available (Caldas et al. 2020; Qi et al. 2019; Solano 2017; Wang, Hou, et al. 2019). Melanin or melanin-based nanoparticles also exhibit excellent antioxidant activity and are potent quenching agents for reactive oxygen species (ROS) and free radicals. Liu et al. (2017) tested synthetic PDMN as an anti-inflammatory and neuroprotective agent in a rat model. They found that injecting nanoparticles into rats reduced their defenses against ischemic stroke and inflammation. Melanin-based nanoparticles have also been

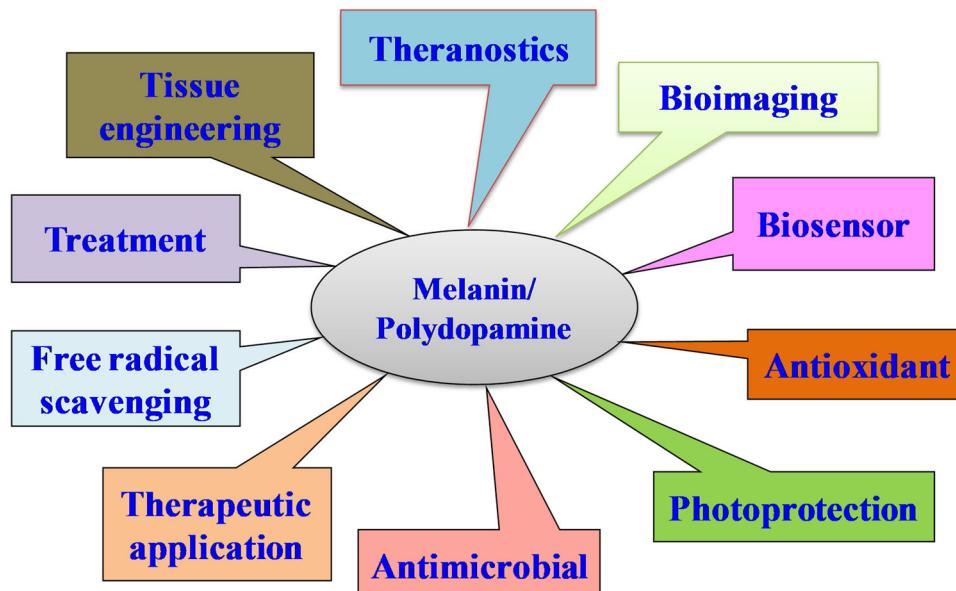


Figure 15. Various biomedical applications of melanin or melanin-like nanoparticles.

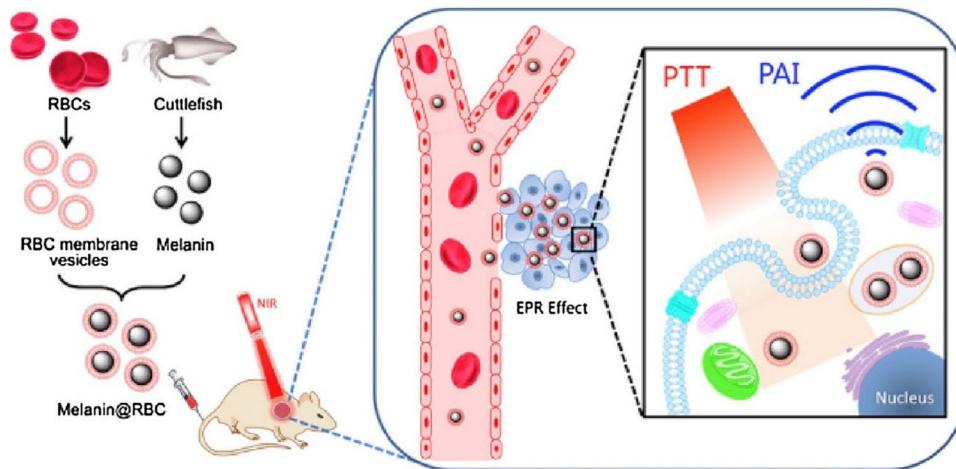


Figure 16. Schematic illustration of the function of RBC membrane camouflaged MNP for enhanced photothermal therapy (Jiang et al. 2017).

proposed for use as carriers of hemoglobin-based oxygen. PD coating of hemoglobin has a vital function to help hemoglobin maintain high oxygen affinity by inhibiting hemoglobin oxidation to met-hemoglobin (Wang, Zhang, et al. 2017). The anti-tumor activity of PDMN has also been reported. PDMN can kill tumor cells (such as HeLa and 4T1 cells) in animal models with a short irradiation laser time (Liu et al. 2013). Another great advantage of PDMN is its excellent biocompatibility and can remain in the blood for several months, so the investigation process can be repeated without duplicating the injection process (Liu et al. 2013). Shi et al. (2018) prepared dopamine-based fluorescent starch nanoparticles for fluorescence imaging applications. They showed that the PD-based starch nanoparticles are biocompatible and can be used as fluorescence probes and carriers to deliver active biological components. It has also been reported that MRI, antioxidants, or photothermal therapies have been improved in the presence of PDMN-based nanoparticles (PDMN conjugated with other materials) (Wang, Hou, et al. 2019). PDMN-based nanoparticles have also been

used as carriers for certain drugs (Araújo et al. 2014). It has been reported that melanin can act as a potential pH-reactive drug release device. Melanin has been shown to respond efficiently to pH to regulate drug release (Araújo et al. 2014). The advantage of using melanin is that it is readily available and can be used without structural modifications. There is also a report on melanin drug conjugate adsorption binding affinity, which is beneficial for studying drug assembly in the skin, hair, or tissues where melanin pigments are present (Liopo, Su, and Oraevsky 2015). Jiang et al. (2017) used natural MNP for enhanced photothermal therapy. After being coated with a red blood cell (RBC) membrane, MNP could generate MNP-RBC nanoparticles, effectively improving blood retention and tumor accumulation *in vivo*. The MNP-RBC nanoparticles had excellent photoacoustic imaging property, excellent photothermal conversion capability, and showed superior antitumor efficacy in A549 tumor-bearing mice compared to MNP (Figure 16). Bettinger et al. (2009) prepared biocompatible and biodegradable semiconducting melanin-based films for nerve

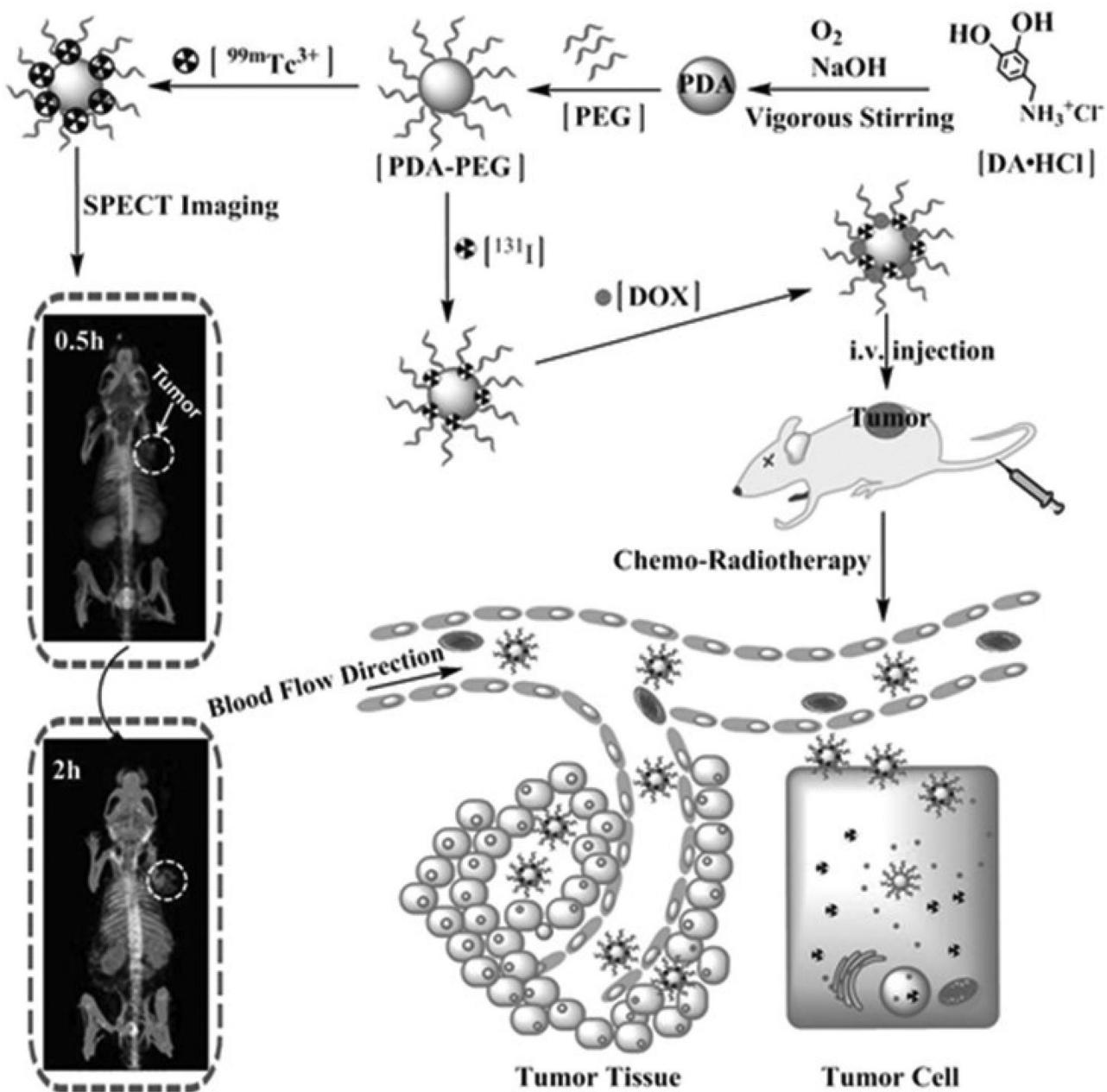


Figure 17. Schematic diagram to show radionuclides (^{99m}Tc or ¹³¹I) labeled poly(ethylene glycolylated PDMN with doxorubicin loading for single-photon emission computed tomography imaging and combined radiotherapy (Zhong et al. 2015).

tissue engineering. They showed that the melanin implantation in rats' peripheral nerves made a foreign body response, and the effect was positive for nerve tissue similar to silicon. Another important fact is that the transplanted melanin decomposed almost entirely after 8 weeks. These results suggest excellent biocompatibility and biodegradability of melanin.

Melanin has also been widely used in melanin-based contrast agents for photoacoustic imaging. There are already several melanin-based imaging probes described with specific properties suitable for photoacoustic imaging (Solano 2017). Zhong et al. (2015) have developed a PD-based nano-carrier to treat cancer using combined radioisotope therapy and chemotherapy. They showed that the PD-based nano-carriers exhibit excellent physiological stability and prolonged blood circulation time, and the unique radiolabeling

and molecular loading behaviors of PD. The drug-loaded and radioisotope-labeled PDMN was a safe and effective nano-drug that could be used in combination therapy of cancer (Figure 17). Yan et al. (2016) reported the role of MNP as an effective endogenous nano-drug effective in treating iron overload (Figure 18). They showed that MNP had better efficacy in iron excretion than the most commonly used deferoxamine agent. Zhang, Zhao, et al. (2017) reported effective photothermal chemotherapy with pH-responsive polymer-coated drug-loaded MLNPs. The authors concluded that polymer-coated drug-loaded MLNPs have many useful properties such as pH-responsiveness, sustained release, and chemo-thermal ability that can be used to treat cancer. In another report, PEG-MNP with a size of 7–10 nm exhibited excellent effects in tumor vasculature evaluation and response to anti-angiogenic treatment (Longo, Stefania,

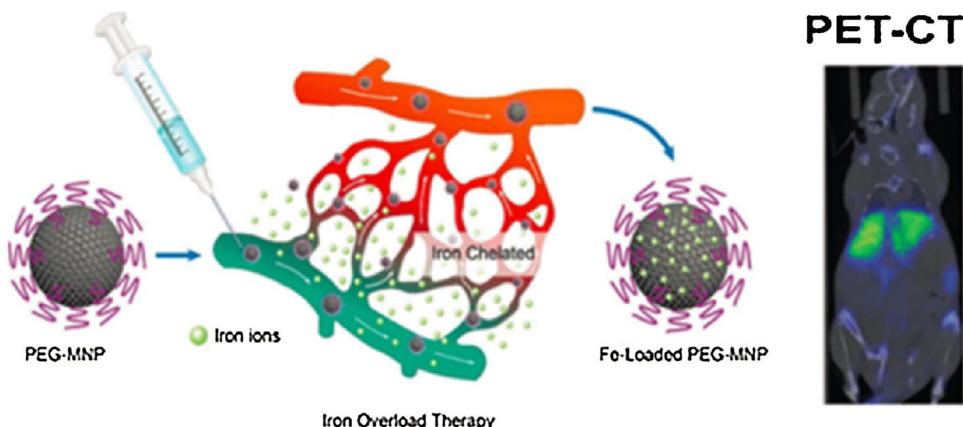


Figure 18. Schematic diagram of utilizing ultrasmall PEG-MNPs as metal-ion scavengers to excrete excess iron for overload therapy (Yan et al. 2016).

Aime, et al. 2017). Chen et al. (2016) developed a PD-tunable nanocomposite for dual-mode magnetic resonance imaging-induced chemo-photothermal synergistic therapy. The authors explained that the developed nanocomposite helps with MRI-induced photothermal enhancement drug delivery. The nanocomposite also showed remote laser-triggered release property and excellent chemo-thermal synergistic treatment. PDMN loaded with Fe^{3+} of $<100\text{ nm}$ size offers a proper application in photoacoustic and magnetic resonance imaging (Ju et al. 2011). The melanin molecule was biocompatible and showed good photoacoustic imaging potential with more light absorption than the near-infrared region's surrounding skin. PEG-PDMN, decorated with citraconic amide, showed excellent optoacoustic cancer imaging properties (Ju et al. 2016). Ju et al. (2016) found that the aggregation of MLNP enhanced photoacoustic signals in the near-infrared region of biological tissue. On the other hand, pegylated polydopamine nanoparticles (PEG-PDMN) of size 50 nm show a useful application in 3-dimensional optoacoustic vascular imaging (Liopo, Su, and Oraevsky 2015). Liopo, Su, and Oraevsky (2015) showed that the optoacoustic efficiency of MNP is similar to that of gold nanoparticles, a commonly known optoacoustic agent. The results indicate that MNP is an excellent nanoprobe for photoacoustic imaging. Zhang et al. (2012) studied the cell imaging potency of the polydopamine fluorescent organic nanoparticles. The prepared PDMN-based nanoparticles were water-soluble and exhibited excellent biocompatibility without significant cytotoxicity. The PDMN-based nanoparticles were accumulated in the cells and were very efficient as fluorescence imaging. Potential biomedical applications of melanin or conjugated melanin nanomaterials have a good impact, suggesting that they can also be used in theragnostic.

7.4. Packaging film

In general, food packaging provides a passive barrier for protecting food from many factors such as heat, UV-light, water, oxygen, external pressure, etc. Packaging also helps extend the shelf-life of food and secure food safety by preventing microorganisms' growth. Active packaging has advantages over conventional packaging as an alternative to

the direct addition of synthetic active compounds (e.g., preservatives) to food. Also, concerns over the use of artificial additives that can adversely affect health have recently increased. To this end, active packaging can be considered a platform that protects food from external factors and extends the shelf-life (Vilela et al. 2018). The addition of synthetic antioxidants such as butylated hydroxyanisole can potentially prevent lipid peroxidation and improve the shelf life of foods, but it causes many side effects to the human body and raises questions about the safety of the product (Domínguez et al. 2018). Concerns over synthetic chemically active packaging have spurred research into the use of innovative alternatives such as bioactive compounds obtained from natural sources (Sharma et al. 2021). For this purpose, natural antioxidants such as natural extracts, polyphenols, essential oils, and natural plant compounds can be an excellent choice to protect food quality and safety. In this regard, a variety of bioactive functional materials have been used to make active packaging films (Atarés and Chiralt 2016; Rai et al. 2019; Roy and Rhim 2020a, 2020b; Roy, Kim, and Rhim 2021; Sharma et al. 2021; Vilela et al. 2018; Yong and Liu 2020). Recently, the use of melanin has attracted a lot of attention to developing active food packaging films. Melanin's strong UV protection, intense antioxidant activity, and moderate antibacterial activity make it an ideal candidate for use as an active packaging material. Various polymers have been used so far for the manufacture of active packaging films containing melanin. Due to bio-based polymers' biodegradability and renewability, they are advantageous over commonly used petroleum-based non-biodegradable plastics. Various biopolymers such as carbohydrates, proteins, and their combination, including starch, carrageenan, agar, alginate, chitosan, cellulose, whey protein, gelatin, etc., were used. Also, bioplastics and commercial synthetic polymers such as polyurethane, PLA, PVA, linear low-density polyethylene, poly(butylene adipate-co-terephthalate), polypropylene, polyhydroxy butyrate, etc. have been used for the preparation of active food packaging films.

Also, various types of polymers or biopolymers have been used to develop melanin or MNP-based composite films, and the results of studies on functional films using melanin are summarized in Table 3. Melanin was added to poly(lactic acid) (PLA) film for active packaging applications

Table 3. Melanin or MNP/MLNP incorporated polymers based composite film.

Melanin	Polymers	Properties	References
Fungal melanin	PLA	Antioxidant activity	Łopusiewicz, Jedra, and Mizielińska 2018a
Sepia melanin (natural) and dopamine (synthetic)	PVA	Thermal stability	Dong et al. 2014
Dopamine	PVA	Mechanical properties	Wang et al. 2015
Dopamine	PVA	UV-shielding	Wang, Zhang, et al. 2017
Sepia ink	PVA	UV-shielding properties and photostability	Wang, Li, Ma, et al. 2016
Sepia ink and Dopamine	Bisphenol A PC	UV-shielding properties and photostability	Wang et al. 2018
Sepia ink	Polyurethane	Mechanical properties (Strength and toughness)	Wang, Li, Wang, et al. 2016
Sepia ink	Carageenan	Antioxidant, UV-barrier property, thermal stability, and mechanical property	Roy and Rhim 2019d
Sepia ink	Agar	Antioxidant, UV-shielding, mechanical properties, and water vapor barrier property	Roy and Rhim 2019b
Dopamine	Chitosan	Antioxidant, UV-shielding, hydrophobicity, and mechanical properties	Roy, Van Hai, et al. 2020
Sepia ink	Cellulose nanofiber	UV-shielding, mechanical and antioxidant properties	Roy, Kim, et al. 2020
Sepia ink	Gelatin	Antioxidant, UV-blocking, thermal stability, mechanical property, and water vapor barrier property	Shankar, Wang, et al. 2019
Sepia ink	Alginate/PVA	UV-blocking, thermal stability, mechanical property, and water vapor barrier property	Yang et al. 2020
Sepia ink and synthetic eumelanin	linear low-density polyethylene	UV-shielding and photostability	Di Mauro, Li, et al. 2019
<i>Tetyrina citrina</i>	Polyhydroxy butyrate	Antioxidant and antimicrobial activity	Kiran et al. 2017
Sepia ink	Polypropylene and poly(butylene adipate-co-terephthalate)	UV-shielding and mechanical properties	Bang, Shankar, and Rhim 2020
Dopamine	Poly(butylene adipate-co-terephthalate)	UV-blocking properties	Xing et al. 2019
Watermelon (<i>Citrullus lanatus</i>) seed	Whey Protein Concentrate	UV blocking, Water vapor barrier, Mechanical properties, Antioxidant activity	Łopusiewicz et al. 2020

(Łopusiewicz, Jedra, and Mizielińska 2018a). The addition of melanin improved the mechanical and gas barrier properties of PLA film. The incorporation of the black pigment to PLA also exhibited improved antioxidant and antimicrobial properties of PLA film. The same research group also reported on the whey protein-based active packaging film blended with melanin extracted from watermelon (*Citrullus lanatus*) seeds (Łopusiewicz et al. 2020). They found that bioactive functional materials' addition has improved many physical properties like UV blocking, water vapor barrier, and mechanical properties of the composite film. Moreover, the inclusion of melanin significantly improved the film's antioxidant activity without showing a cytotoxic effect on the L929 murine fibroblast cell line. Dong et al. (2014) prepared melanin incorporated poly(vinyl alcohol) (PVA) film using a solution casting method. They found that PVA film's thermal stability increased significantly by the addition of natural and synthetic melanin. Synthetic melanin synthesized from dopamine showed a higher effect than natural melanin. Wang et al. (2015) showed that the PVA film's mechanical performance was greatly improved by adding MNP. Wang, Zhang, et al. (2017) also found that the UV shielding properties of PVA film increased substantially by adding synthetic bioinspired dopamine-melanin hollow and solid nanoparticles. They asserted that the hollow form of dopamine melanin nanoparticles is a very potential UV absorber for next-generation transparent UV shielding materials. Wang, Li, Ma, et al. (2016) also showed that the addition of sepia melanin to the PVA film improved UV-shielding properties and photostability of the PVA film. They also found that the addition of 0.5 wt% melanin to the PVA film blocked 98.7% UV light below 300 nm with high transparency in visible light. It has been observed that the addition of melanin to PVA reduced the bandgap energy from 5.01

to 3.43 eV, indicating the formation of a charge-transfer complex between melanin and PVA. Besides, melanin has been shown to have an excellent ability to resist photodegradation of synthetic dye like Rhodamine B. The photostability of PVA/melanin film depends on forming a stable charge-transfer complex, photothermal conversion, and radical scavenging capacity of natural melanin. (Wang, Li, Ma, et al. 2016). Wang et al. (2018) tested the effect of melanin particle size on the optical properties of the bisphenol A polycarbonate film-based nanocomposite films. They found that the smaller the nanoparticle size, the higher the efficiency in UV-shielding and visible light transparency properties. Melanin incorporated polyurethane-based nanocomposites film has also been prepared using in situ polymerization (Wang, Li, Wang, et al. 2016). They found that the tensile strength and toughness of the film increased significantly by the addition of natural melanin. Roy and Rhim (2019d) prepared a carageenan-based nanocomposite film incorporated with MNP isolated from sepia. They also found that incorporating MNP enhanced the UV-barrier property, thermal stability, and mechanical property of the film. Besides, the nanocomposite film exhibited potent antioxidant activity and some antibacterial activity against foodborne pathogenic bacteria. The strong UV-barrier and antioxidant properties of MNP-added carageenan film are shown in Figure 19. The addition of 2 wt% MNP to the carageenan-based film blocked ~ 97% UV light, and the addition of MNP induced strong antioxidant activity to the carageenan-based composite film. They also showed that the antioxidant activity of MNP was as high as that of ascorbic acid, a natural antioxidant. Roy & Rhim (2019b) also reported agar/MNP functional nanocomposite film for active packaging applications. They found the addition of MNP in the agar film significantly improved the UV-shielding, mechanical, and water

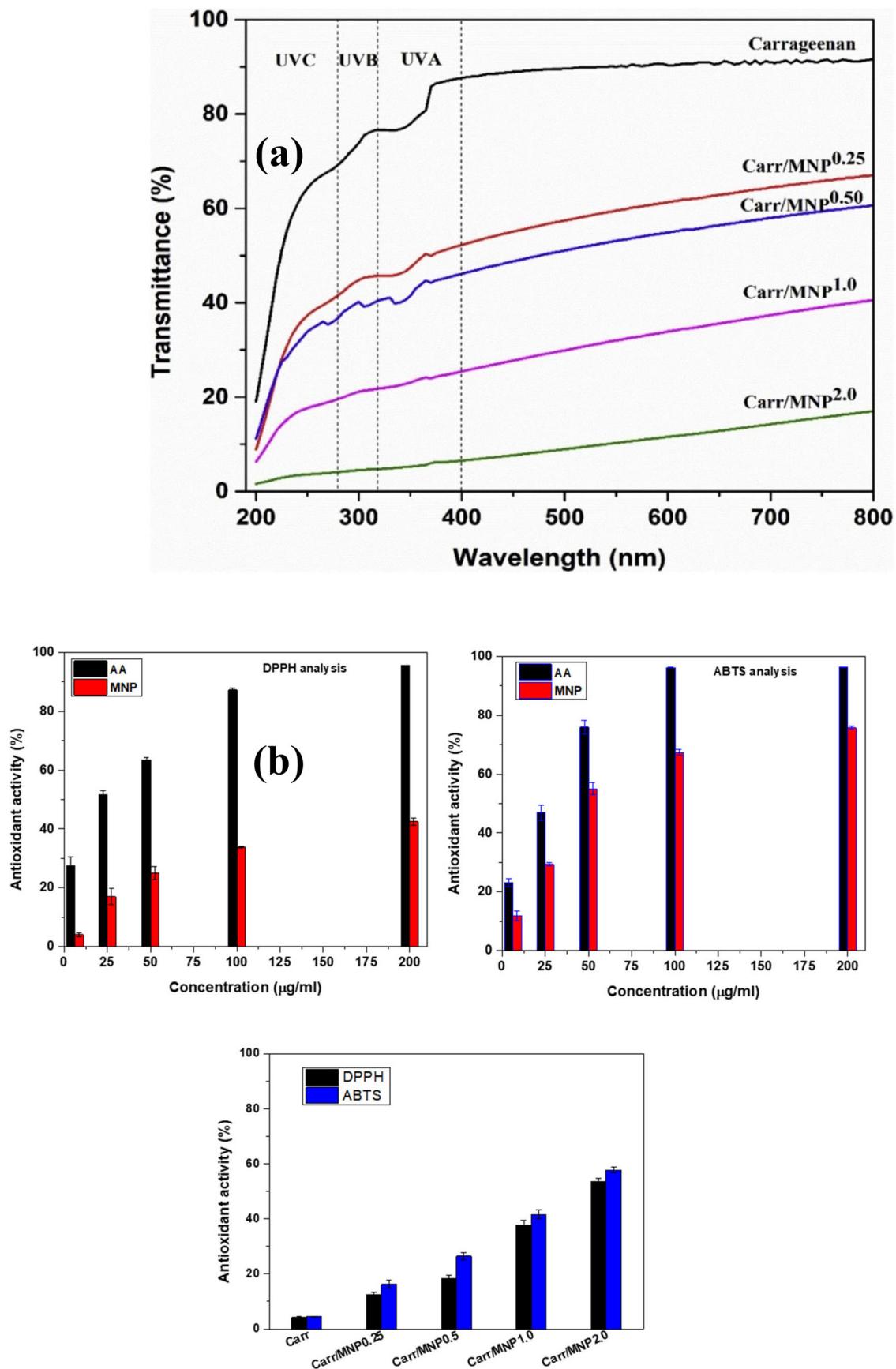


Figure 19. (a) The transmittance spectra of carrageenan and carrageenan/MNP nanocomposite films. (b) Antioxidant activity of MNP, ascorbic acid, and carrageenan/MNP nanocomposite films (Roy and Rhim 2019d).

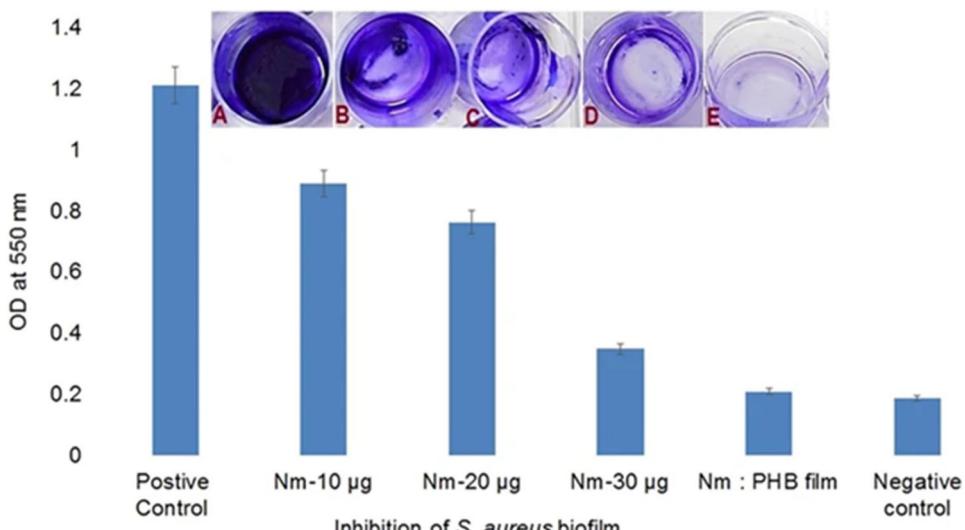


Figure 20. Antibiofilm activity of nano-melanin and in nano-melanin (Nm)/polyhydroxy butyrate (PHB) composite by the well microtiter plate assay. Insets show the top-down view of well plate assay. (A) Control biofilm of *S. aureus*. (B–D) Wells coated with 10, 20, and 30 µg/ml of Nm, respectively. (E) Wells coated with Nm/PHB composite (Kiran et al. 2017).

vapor barrier property of the film with high antioxidant activity. Shankar, Wang, et al. (2019) also prepared the MNP reinforced gelatin-based nanocomposite film for packaging applications. They have shown that the addition of MNP in gelatin significantly increased UV-blocking, thermal stability, mechanical property, and water vapor barrier property of the composite film. Also, the addition of MNP provided an intense antioxidant activity to the gelatin-based composite film. Shankar, Bang, et al. (2019) prepared a low-density polyethylene film blended with melanin, zinc oxide, and grapefruit seed extract using an extrusion blowing method. The authors found that the UV-barrier and thermal properties were improved significantly by the addition of the fillers. They tested the composite film-coated wrapping paper for the application of “gimbap” (Korean rolled rice) packaging and showed that the composite film-coated wrapping paper had a sufficient water and oil resistance property and appreciable antimicrobial activity to inhibit the growth of coliform bacteria in gimbap. Recently, Roy, Kim, et al. (2020) prepared hardwood cellulose nanofiber-based nanocomposite film by the incorporation of melanin. They showed that the inclusion of melanin improved the UV-shielding, mechanical, and antioxidant properties of the cellulose nanofiber-based nanocomposite films. The authors showed that the addition of MNP in the cellulose-based film blocked ~96% of UV light. Roy, Van Hai, et al. (2020) prepared and characterized synthetic melanin-like nanoparticles reinforced chitosan-based nanocomposite films. The authors showed that the addition of melanin-like nanoparticles to chitosan significantly improved the UV-shielding, hydrophobicity, antioxidant activity, and mechanical properties of the nanocomposite films. Recently, Xing et al. (2019) prepared the melanin-lignin core-shell nanoparticles and used the nanoparticles to prepare the poly(butylene adipate-co-terephthalate) based biodegradable UV-blocking film. They developed core-shell nanoparticles using lignin and melanin, and found that they were compatible and durable. The nanoparticles were used to make a biodegradable film and

found that the incorporation of bioactive nanoparticles significantly improved the thermal stability and mechanical properties. In addition, the composite film completely blocked UV-A and blocked 80% of UV-B light, thereby exhibiting very remarkable UV shading properties. The authors suggested the film with improved mechanical strength with UV-blocking properties could be used in food packaging and agriculture. Łopusiewicz, Jędra, and Mizielińska (2018b) used melanin as functional coating material to prevent the oxidation of pork lard. The same authors also reported the preparation of active packaging film using gelatin and fungal modified melanin (Łopusiewicz, Jędra, and Mizielińska 2018c). They showed that the incorporation of fungal melanin into gelatin did not significantly affect the physical barrier (mechanical, thermal, water vapor barrier), but improved oxygen barrier properties and markedly improved UV-light barrier properties, which may be useful for active packaging applications. In another report, nano-melanin was prepared using melanin extracted from the marine sponge *Tetirina citrina* and then added to polyhydroxy butyrate (PHB) to produce an active functional film (Kiran et al. 2017). They found that the prepared film was thermostable and showed strong protective activity against drug-resistant bacteria. They also found that the nano-melanin and its composite film are very effective in preventing biofilm formation (Figure 20). Not only nano-melanin but also nano-melanin reinforced PHB composite showed complete inhibition of *S. aureus* biofilm formation. The well image (inset of Figure 20) also showed the clear view of antibiofilm activity of the composite film.

Yang et al. (2020) also described the incorporation of naturally isolated MNP in PVA/alginate composite film. They showed that the addition of MNP in PVA/alginate composite films significantly improved mechanical, UV-vis light barrier, and thermal insulating properties. In particular, the addition of MNP exhibited excellent UV-light shielding properties of PVA/alginate-based film (Figure 21). The UV-shielding phenomenon was well proven in Figure 21, and it

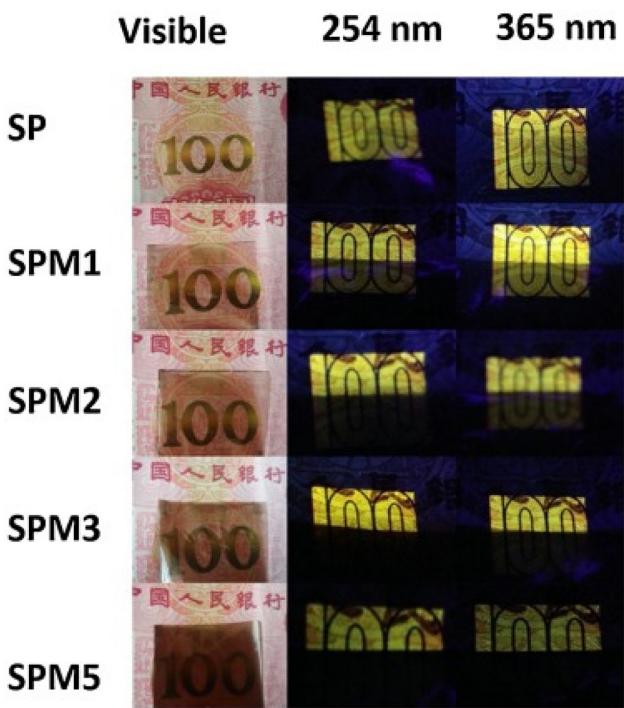


Figure 21. UV-blocking effect of alginate/PVA/melanin-based composite films (here SP-Alginate/PVA and SPM 1–5 refers to the percentage of MNP) (Yang et al. 2020).

can be seen that the fluorescent number (100) was greatly affected by the UV light. The melanin-containing PVA/alginate film gradually began to darken depending on melanin's content in the film. Di Mauro, Li, et al. (2019) prepared synthetic and natural melanin incorporated linear low-density polyethylene films using melt-extrusion followed by a thermocompression method. They found that even a small amount of melanin (0.8 wt%) can effectively enhance the UV absorption up to one order of magnitude in the UVA range. It was also observed that the melanin-based film was stable for a long time (144 days) under long-term UV irradiation. Recently, Bang, Shankar, and Rhim (2020) produced a melanin-incorporated polypropylene/poly(butylene adipate-co-terephthalate) blend film using an extrusion casting method. The composite film showed high UV-barrier property and they applied the film for preventing greening of potato. They packed the potato with the composite film (test group) and the control film (PP only) for comparison and stored under fluorescent light at room temperature ($23 \pm 2^\circ\text{C}$) for 6 days. The potato of test group produced 63% less chlorophyll than that of the control group, indicating the composite film was very effective in preventing greening of potato. It is apparent that the incorporation of melanin or MNP to biopolymer or other polymer-based films significantly improves physical and functional properties of the film and the MNP reinforced nanocomposite films are likely to be used in active food packaging applications.

7.5. Cosmetics

Today, natural colorants and antioxidants are becoming increasingly popular among consumers because synthetic pigments and antioxidants are often perceived as undesirable or harmful. The

recent advent of nanotechnology has also increased interest in the use of safe and biocompatible melanin or nano-melanin in food and biomedical applications. The antioxidant properties of melanin are beneficial and can be applied to cosmetics to protect the skin. Biologically produced melanin can inhibit peroxidative damage and acts similar to natural antioxidants like vitamin C and vitamin E. In cosmetics, melanin is mainly used for skin conditioning, skin protection, and anti-aging agents. Melanin also plays an essential role in skin coloring and tanning and can also be used as a sunscreen. Natural melanin has superior peroxidative damage-inhibiting activity compared to synthetic melanin. Therefore, melanin is used alone or in combination with other natural antioxidants as a cosmetic light protector (Kalka et al. 2000; Liberti et al. 2020). Melanin is used as an active agent in sunscreen and also acts as an antiaging agent. Melanin also helps reduce skin inflammation caused by chemical agents. Besides, melanin helps to stop the formation of skin and remove scar marks. The melanin present in the pigment is very safe and exhibits high coloration and high saturation (Shinkichi, Takekoshi, and Arai 1993).

8. Conclusions

Melanin is a group of natural, inexpensive, abundant, and nontoxic pigment materials with numerous applications due to its various physicochemical properties. Melanin can be easily extracted from multiple natural sources or chemically synthesized. Although relatively well-known for melanin and melanin-like compounds, studies on melanin's structure and function are still required to use melanin-based materials. Melanin plays a perfect role in UV-light shielding, as well as in photoprotection. Melanin and MNP also have some antimicrobial activity and strong antioxidant properties, making them suitable filler materials for making functional composite films. Melanin has also been used as a green producer of metallic nanoparticles and as a stabilizing agent. Melanin, especially nano-melanin, with functional properties such as UV-barrier, antioxidant, antimicrobial, and coloring properties, has a high potential in various industrial uses such as food packaging and biomedical and cosmetics industries. However, more research is needed for melanin's scale-up process, including optimized extraction and purifications of natural melanin and synthetic melanin-like materials. More attention should also be paid to the toxicity of melanin or melanin-like compounds because few reports suggested that the PD-based materials showed some unwanted side effects (Mrówczyński, Bunge, and Liebscher 2014). However, there are no such safety problems in food packaging applications.

Abbreviations

MNPs	melanin nanoparticles
MLNP	melanin-like nanoparticles
DHI	5,6-dihydroxyindole
DHICA	5,6-dihydroxyindole-2-carboxylic acid
PD	polydopamine
PDMN	polydopamine melanin nanoparticles
UVA	ultraviolet A
UVB	ultraviolet B
DOPA	3,4-dihydroxyphenylalanine

AgNPs	silver nanoparticles
AuNPs	gold nanoparticles
SERS	surface-enhanced Raman scattering
PVA	poly(vinyl alcohol)
PLA	poly(lactic acid)
PHB	polyhydroxy butyrate
ROS	reactive oxygen species

Disclosure statement

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References

- Abdel-Malek, Z. A., A. L. Kadekaro, and V. B. Swope. 2010. Stepping up melanocytes to the challenge of UV exposure. *Pigment Cell & Melanoma Research* 23 (2):171–86. doi: [10.1111/j.1755-148X.2010.00679.x](https://doi.org/10.1111/j.1755-148X.2010.00679.x).
- Agar, N. S., G. M. Halliday, R. S. Barnetson, H. N. Ananthaswamy, M. Wheeler, and A. M. Jones. 2004. The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: A role for UVA in human skin carcinogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 101 (14):4954–9. doi: [10.1073/pnas.0401141101](https://doi.org/10.1073/pnas.0401141101).
- Apte, M., G. Girme, A. Bankar, A. Ravikumar, and S. Zinjarde. 2013. 3,4-dihydroxy-L-phenylalanine-derived melanin from *Yarrowia lipolytica* mediates the synthesis of silver and gold nanostructures. *Journal of Nanobiotechnology* 11:2. doi: [10.1186/1477-3155-11-2](https://doi.org/10.1186/1477-3155-11-2).
- Apte, M., G. Girme, R. Nair, A. Bankar, A. Ravi Kumar, and S. Zinjarde. 2013. Melanin mediated synthesis of gold nanoparticles by *Yarrowia lipolytica*. *Materials Letters* 95:149–52. doi: [10.1016/j.matlet.2012.12.087](https://doi.org/10.1016/j.matlet.2012.12.087).
- Apte, M., D. Sambre, S. Gaikawad, S. Joshi, A. Bankar, A. R. Kumar, and S. Zinjarde. 2013. Psychrotrophic yeast *Yarrowia lipolytica* NCYC 789 mediates the synthesis of antimicrobial silver nanoparticles via cell-associated melanin. *AMB Express* 3 (1):32. doi: [10.1186/2191-0855-3-32](https://doi.org/10.1186/2191-0855-3-32).
- Araújo, M., R. Viveiros, T. R. Correia, I. J. Correia, V. D. B. Bonifácio, T. Casimiro, and A. Aguiar-Ricardo. 2014. Natural melanin: A potential pH-responsive drug release device. *International Journal of Pharmaceutics* 469 (1):140–5. doi: [10.1016/j.ijpharm.2014.04.051](https://doi.org/10.1016/j.ijpharm.2014.04.051).
- Atarés, L., and A. Chiralt. 2016. Essential oils as additives in biodegradable films and coatings for active food packaging. *Trends in Food Science & Technology* 48:51–62. doi: [10.1016/j.tifs.2015.12.001](https://doi.org/10.1016/j.tifs.2015.12.001).
- Ball, V. 2017. Composite materials and films based on melanins, polydopamine, and other catecholamine-based materials. *Biomimetics* 2 (4):12. doi: [10.3390/biomimetics2030012](https://doi.org/10.3390/biomimetics2030012).
- Ball, V., D. Del Frari, M. Michel, M. J. Buehler, V. Tonazzzo, M. K. Singh, J. Gracio, and D. Ruch. 2012. Deposition mechanism and properties of thin polydopamine films for high added value applications in surface science at the nanoscale. *BioNanoScience* 2 (1): 16–34. doi: [10.1007/s12668-011-0032-3](https://doi.org/10.1007/s12668-011-0032-3).
- Bang, Y.-J., S. Shankar, and J.-W. Rhim. 2020. Preparation of polypropylene/poly(butylene adipate-co-terephthalate) composite films incorporated with melanin for prevention of greening of potatoes. *Packaging Technology and Science* 33:433–41. doi: [10.1002/pts.2525](https://doi.org/10.1002/pts.2525).
- Barclay, T. G., H. M. Hegab, S. R. Clarke, and M. Ginic-Markovic. 2017. Versatile surface modification using polydopamine and related polycatecholamines: Chemistry, structure, and applications. *Advanced Materials Interfaces* 4 (19):1601192. doi: [10.1002/admi.201601192](https://doi.org/10.1002/admi.201601192).
- Bernardus Mostert, A., B. J. Powell, I. R. Gentle, and P. Meredith. 2012. On the origin of electrical conductivity in the bio-electronic material melanin. *Applied Physics Letters* 100 (9):093701. doi: [10.1063/1.3688491](https://doi.org/10.1063/1.3688491).
- Bettinger, C. J., J. P. Bruggeman, A. Misra, J. T. Borenstein, and R. Langer. 2009. Biocompatibility of biodegradable semiconducting melanin films for nerve tissue engineering. *Biomaterials* 30 (17): 3050–7. doi: [10.1016/j.biomaterials.2009.02.018](https://doi.org/10.1016/j.biomaterials.2009.02.018).
- Bin, L., L. Wei, C. Xiaohong, J. Mei, and D. Mingsheng. 2012. In vitro antibiofilm activity of the melanin from *Auricularia auricula*, an edible jelly mushroom. *Annals of Microbiology* 62 (4):1523–30. doi: [10.1007/s13213-011-0406-3](https://doi.org/10.1007/s13213-011-0406-3).
- Blois, M. S., A. B. Zahlan, and J. E. Maling. 1964. Electron spin resonance studies on melanin. *Biophysical Journal* 4:471–90. doi: [10.1016/S0006-3495\(64\)86797-7](https://doi.org/10.1016/S0006-3495(64)86797-7).
- Borovanský, J. 1996. Free radical activity of melanins and related substances: Biochemical and pathobiochemical aspects. *Sborník Lekarský* 97 (1):49–70.
- Borovanský, J., and P. A. Riley. 2011. Physiological and pathological functions of melanosomes. In *Melanins and melanosomes*, eds J. Borovanský and P. A. Riley, 343–81. Weinheim, Germany: Wiley. doi: [10.1002/9783527636150.ch12](https://doi.org/10.1002/9783527636150.ch12).
- Brenner, M., and V. J. Hearing. 2008. The protective role of melanin against UV damage in human skin. *Photochemistry and Photobiology* 84 (3):539–49. doi: [10.1111/j.1751-1097.2007.00226.x](https://doi.org/10.1111/j.1751-1097.2007.00226.x).
- Brumbaugh, J. A. 1968. Ultrastructural differences between forming eumelanin and pheomelanin as revealed by the pink-eye mutation in the fowl. *Developmental Biology* 18 (4):375–90. doi: [10.1016/0012-1606\(68\)90047-X](https://doi.org/10.1016/0012-1606(68)90047-X).
- Caldas, M., A. C. Santos, F. Veiga, R. Rebelo, R. L. Reis, and V. M. Correlo. 2020. Melanin nanoparticles as a promising tool for biomedical applications – A review. *Acta Biomaterialia* 105:26–43. doi: [10.1016/j.actbio.2020.01.044](https://doi.org/10.1016/j.actbio.2020.01.044).
- Chen, H., L. Zhao, D. Chen, and W. Hu. 2015. Stabilization of gold nanoparticles on glass surface with polydopamine thin film for reliable LSPR sensing. *Journal of Colloid and Interface Science* 460: 258–63. doi: [10.1016/j.jcis.2015.08.075](https://doi.org/10.1016/j.jcis.2015.08.075).
- Chen, Y., K. Ai, J. Liu, X. Ren, C. Jiang, and L. Lu. 2016. Polydopamine-based coordination nanocomplex for T1/T2 dual mode magnetic resonance imaging-guided chemo-photothermal synergistic therapy. *Biomaterials* 77:198–206. doi: [10.1016/j.biomaterials.2015.11.010](https://doi.org/10.1016/j.biomaterials.2015.11.010).
- Chiarelli-Neto, O., C. Pavani, A. S. Ferreira, A. F. Uchoa, D. Severino, and M. S. Baptista. 2011. Generation and suppression of singlet oxygen in hair by photosensitization of melanin. *Free Radical Biology & Medicine* 51 (6):1195–202. doi: [10.1016/j.freeradbiomed.2011.06.013](https://doi.org/10.1016/j.freeradbiomed.2011.06.013).
- Cho, S., W. Park, and D.-H. Kim. 2017. Silica-coated metal chelating-melanin nanoparticles as a dual-modal contrast enhancement imaging and therapeutic agent. *ACS Applied Materials & Interfaces* 9 (1): 101–11. doi: [10.1021/acsami.6b11304](https://doi.org/10.1021/acsami.6b11304).
- Chongkae, S., J. D. Nosanchuk, K. Pruksaphon, A. Laliam, S. Pornsuwan, and S. Youngchim. 2019. Production of melanin pigments in saprophytic fungi in vitro and during infection. *Journal of Basic Microbiology* 59 (11):1092–104. doi: [10.1002/jobm.201900295](https://doi.org/10.1002/jobm.201900295).
- Chu, M., W. Hai, Z. Zhang, F. Wo, Q. Wu, Z. Zhang, Y. Shao, D. Zhang, L. Jin, and D. Shi. 2016. Melanin nanoparticles derived from a homology of medicine and food for sentinel lymph node mapping and photothermal in vivo cancer therapy. *Biomaterials* 91:182–99. doi: [10.1016/j.biomaterials.2016.03.018](https://doi.org/10.1016/j.biomaterials.2016.03.018).
- Domínguez, R., F. J. Barba, B. Gómez, P. Putnik, D. Bursać Kovacević, M. Pateiro, E. M. Santos, and J. M. Lorenzo. 2018. Active packaging films with natural antioxidants to be used in meat industry: A

- review. *Food Research International* 113:93–101. doi: [10.1016/j.foodres.2018.06.073](https://doi.org/10.1016/j.foodres.2018.06.073).
- d'Ischia, M., A. Napolitano, V. Ball, C.-T. Chen, and M. J. Buehler. 2014. Polydopamine and eumelanin: From structure-property relationships to a unified tailoring strategy. *Accounts of Chemical Research* 47 (12):3541–50. doi: [10.1021/ar500273y](https://doi.org/10.1021/ar500273y).
- d'Ischia, M., A. Napolitano, A. Pezzella, P. Meredith, and M. Buehler. 2020. Melanin biopolymers: Tailoring chemical complexity for materials design. *Angewandte Chemie International Edition* 59 (28): 11196–205. doi: [10.1002/anie.201914276](https://doi.org/10.1002/anie.201914276).
- d'Ischia, M., K. Wakamatsu, A. Napolitano, S. Briganti, J.-C. Garcia-Borron, D. Kovacs, P. Meredith, A. Pezzella, M. Picardo, T. Sarna, et al. 2013. Melanins and melanogenesis: Methods, standards, protocols. *Pigment Cell & Melanoma Research* 26 (5):616–33. doi: [10.1111/pcmr.12121](https://doi.org/10.1111/pcmr.12121).
- d'Ischia, M., K. Wakamatsu, F. Cicora, E. Di Mauro, J. C. Garcia-Borron, S. Commo, I. Galván, G. Ghanem, K. Kenzo, P. Meredith, et al. 2015. Melanins and melanogenesis: From pigment cells to human health and technological applications. *Pigment Cell & Melanoma Research* 28 (5):520–44. doi: [10.1111/pcmr.12393](https://doi.org/10.1111/pcmr.12393).
- Di Mauro, E., M. Camaggi, N. Vandooren, C. Bayard, J. De Angelis, A. Pezzella, B. Baloukas, R. Silverwood, A. Ajji, C. Pellerin, et al. 2019. Eumelanin for nature-inspired UV-absorption enhancement of plastics. *Polymer International* 68 (5):984–91. doi: [10.1002/pi.5790](https://doi.org/10.1002/pi.5790).
- Di Mauro, E., X. Li, C. Pellerin, F. Cicora, and C. Santato. 2019. Smart packaging in the sustainability challenge: Eumelanin as a UV-absorption enhancer of polymers. *IEEE Transactions on Nanotechnology* 18:1160–1. doi: [10.1109/TNANO.2019.2941370](https://doi.org/10.1109/TNANO.2019.2941370).
- Diffey, B. L., E. Healy, A. J. Thody, and J. L. Rees. 1995. Melanin, melanocytes, and melanoma. *The Lancet* 346 (8991–8992):1713. doi: [10.1016/S0140-6736\(95\)92882-0](https://doi.org/10.1016/S0140-6736(95)92882-0).
- Dong, C., and Y. Yao. 2012. Isolation, characterization of melanin derived from *Ophiocordyceps sinensis*, an entomogenous fungus endemic to the Tibetan plateau. *Journal of Bioscience and Bioengineering* 113 (4):474–9. doi: [10.1016/j.jbiosc.2011.12.001](https://doi.org/10.1016/j.jbiosc.2011.12.001).
- Dong, H., Z. Liu, H. Zhong, H. Yang, Y. Zhou, Y. Hou, J. Long, J. Lin, and Z. Guo. 2017. Melanin-associated synthesis of SERS-active nanostructures and the application for monitoring of intracellular melanogenesis. *Nanomaterials* 7 (3):70. doi: [10.3390/nano7030070](https://doi.org/10.3390/nano7030070).
- Dong, W., Y. Wang, C. Huang, S. Xiang, P. Ma, Z. Ni, and M. Chen. 2014. Enhanced thermal stability of poly(vinyl alcohol) in presence of melanin. *Journal of Thermal Analysis and Calorimetry* 115 (2): 1661–8. doi: [10.1007/s10973-013-3419-2](https://doi.org/10.1007/s10973-013-3419-2).
- Eisenman, H. C., and A. Casadevall. 2012. Synthesis and assembly of fungal melanin. *Applied Microbiology and Biotechnology* 93 (3): 931–40. doi: [10.1007/s00253-011-3777-2](https://doi.org/10.1007/s00253-011-3777-2).
- El-Batal, A. I., and M. S. S. Al Tamie. 2016. Optimization of melanin production by *Aspergillus oryzae* and incorporation into silver nanoparticles. *Der Pharmacia Lettre* 8 (2):315–33.
- El-Batal, A. I., G. S. El-Sayyad, A. El-Ghamery, and M. Gobara. 2017. Response surface methodology optimization of melanin production by *Streptomyces cyanescens* and synthesis of copper oxide nanoparticles using γ -radiation. *Journal of Cluster Science* 28 (3):1083–112. doi: [10.1007/s10876-016-1101-0](https://doi.org/10.1007/s10876-016-1101-0).
- El-Naggar, N. E.-A., and S. M. El-Ewasy. 2017. Bioproduction, characterization, anticancer and antioxidant activities of extracellular melanin pigment produced by newly isolated microbial cell factories *Streptomyces glaucescens* NEAE-H. *Scientific Reports* 7:42129. doi: [10.1038/srep42129](https://doi.org/10.1038/srep42129).
- ElObeid, A. S., A. Kamal-Eldin, M. A. K. Abdelhalim, and A. M. Haseeb. 2017. Pharmacological properties of melanin and its function in health. *Basic & Clinical Pharmacology & Toxicology* 120 (6): 515–22. doi: [10.1111/bcpt.12748](https://doi.org/10.1111/bcpt.12748).
- Engelen, M., R. Vanna, C. Bellei, F. A. Zucca, K. Wakamatsu, E. Monzani, S. Ito, L. Casella, and L. Zecca. 2012. Neuromelanins of human brain have soluble and insoluble components with dolichols attached to the melanic structure. *PLoS One* 7 (11):e48490. doi: [10.1371/journal.pone.0048490](https://doi.org/10.1371/journal.pone.0048490).
- Fan, B., X. Yang, X. Li, S. Lv, H. Zhang, J. Sun, L. Li, L. Wang, B. Qu, X. Peng, et al. 2019. Photoacoustic-imaging-guided therapy of functionalized melanin nanoparticles: Combination of photothermal ablation and gene therapy against laryngeal squamous cell carcinoma. *Nanoscale* 11 (13):6285–96. doi: [10.1039/c9nr01122f](https://doi.org/10.1039/c9nr01122f).
- Felix, C. C., J. S. Hyde, T. Sarna, and R. C. Sealy. 1978. Interactions of melanin with metal ions. Electron spin resonance evidence for chelate complexes of metal ions with free radicals. *Journal of the American Chemical Society* 100 (12):3922–6. doi: [10.1021/ja00480a044](https://doi.org/10.1021/ja00480a044).
- Forest, S. E., and J. D. Simon. 1998. Wavelength-dependent photoacoustic calorimetry study of melanin. *Photochemistry and Photobiology* 68 (3):296–8. doi: [10.1111/j.1751-1097.1998.tb09684.x](https://doi.org/10.1111/j.1751-1097.1998.tb09684.x).
- Fukuda, M., and K. Sasaki. 1990. Changes in the antibacterial activity of melanin-bound drugs. *Ophthalmic Research* 22 (2):123–7. doi: [10.1159/000267011](https://doi.org/10.1159/000267011).
- Gidianian, S., and P. J. Farmer. 2002. Redox behavior of melanins: Direct electrochemistry of dihydroxyindole-melanin and its Cu and Zn adducts. *Journal of Inorganic Biochemistry* 89 (1-2):54–60. doi: [10.1016/S0162-0134\(01\)00405-6](https://doi.org/10.1016/S0162-0134(01)00405-6).
- Gloster, H. M., and K. Neal. 2006. Skin cancer in skin of color. *Journal of the American Academy of Dermatology* 55 (5):741–60. doi: [10.1016/j.jaad.2005.08.063](https://doi.org/10.1016/j.jaad.2005.08.063).
- González Orive, A., P. Dip, Y. Gimeno, P. Díaz, P. Carro, A. Hernández Creus, G. Benítez, P. L. Schilardi, L. Andrini, F. Requejo, et al. 2007. Electrocatalytic and magnetic properties of ultrathin nanostructured iron-melanin films on Au(111). *Chemistry* 13 (2): 473–82. doi: [10.1002/chem.200600492](https://doi.org/10.1002/chem.200600492).
- Goodman, G., and D. Bercovich. 2008. Melanin directly converts light for vertebrate metabolic use: Heuristic thoughts on birds, Icarus and dark human skin. *Medical Hypotheses* 71 (2):190–202. doi: [10.1016/j.mehy.2008.03.038](https://doi.org/10.1016/j.mehy.2008.03.038).
- Gurme, S. T., C. B. Aware, S. N. Surwase, C. S. Chavan, and J. P. Jadhav. 2019. Synthesis of melanin mediated silver nanoparticles from *Aeromonas* sp. SNS using response surface methodology: Characterization with the biomedical applications and photocatalytic degradation of brilliant green. *Journal of Polymers and the Environment* 27 (11):2428–38. doi: [10.1007/s10924-019-01529-5](https://doi.org/10.1007/s10924-019-01529-5).
- Halder, R. M., and K. M. Bang. 1988. Skin cancer in blacks in the United States. *Dermatologic Clinics* 6 (3):397–405.
- Hou, R., X. Liu, K. Xiang, L. Chen, X. Wu, W. Lin, M. Zheng, J. Fu, and W. Lia. 2019. Characterization of the physicochemical properties and extraction optimization of natural melanin from *Inonotus hispidus* mushroom. *Food Chemistry* 277:533–42. doi: [10.1016/j.foodchem.2018.11.002](https://doi.org/10.1016/j.foodchem.2018.11.002).
- Huang, Y., Y. Li, Z. Hu, X. Yue, M. T. Proetto, Y. Jones, and N. C. Gianneschi. 2017. Mimicking melanosomes: Polydopamine nanoparticles as artificial microparasols. *ACS Central Science* 3 (6):564–9. doi: [10.1021/acscentsci.6b00230](https://doi.org/10.1021/acscentsci.6b00230).
- Hung, Y. C., V. M. Sava, V. A. Blagodarsky, M.-Y. Hong, and G. S. Huang. 2003. Protection of tea melanin on hydrazine-induced liver injury. *Life Sciences* 72 (9):1061–71. doi: [10.1016/S0024-3205\(02\)02348-2](https://doi.org/10.1016/S0024-3205(02)02348-2).
- Hung, Y.-C., V. M. Sava, C. Juang, T. Yeh, W. Shen, and G. Huang. 2002. Gastrointestinal enhancement of MRI with melanin derived from tea leaves (*Thea sinensis* Linn.). *Journal of Ethnopharmacology* 79 (1):75–9. doi: [10.1016/S0378-8741\(01\)00358-0](https://doi.org/10.1016/S0378-8741(01)00358-0).
- Jacobson, E. S., E. Hove, and H. S. Emery. 1995. Antioxidant function of melanin in black fungi. *Infection and Immunity* 63 (12):4944–5. doi: [10.1128/IAI.63.12.4944-4945.1995](https://doi.org/10.1128/IAI.63.12.4944-4945.1995).
- Jacobson, E. S., and S. B. Tinnell. 1993. Antioxidant function of fungal melanin. *Journal of Bacteriology* 175 (21):7102–4. doi: [10.1128/jb.175.21.7102-7104.1993](https://doi.org/10.1128/jb.175.21.7102-7104.1993).
- Jiang, Q., Y. Liu, R. Guo, X. Yao, S. Sung, Z. Pang, and W. Yang. 2019. Erythrocyte-cancer hybrid membrane-camouflaged melanin nanoparticles for enhancing photothermal therapy efficacy in tumors. *Biomaterials* 192:292–308. doi: [10.1016/j.biomaterials.2018.11.021](https://doi.org/10.1016/j.biomaterials.2018.11.021).
- Jiang, Q., Z. Luo, Y. Men, P. Yang, H. Peng, R. Guo, Y. Tian, Z. Pang, and W. Yang. 2017. Red blood cell membrane-camouflaged melanin nanoparticles for enhanced photothermal therapy. *Biomaterials* 143: 29–45. doi: [10.1016/j.biomaterials.2017.07.027](https://doi.org/10.1016/j.biomaterials.2017.07.027).

- Ju, K. Y., J. Kang, J. Pyo, J. Lim, J. H. Chang, and J. K. Lee. 2016. pH-induced aggregated melanin nanoparticles for photoacoustic signal amplification. *Nanoscale* 8 (30):14448–56. doi: [10.1039/c6nr02294d](https://doi.org/10.1039/c6nr02294d).
- Ju, K. Y., Y. Lee, S. Lee, S. B. Park, and J. K. Lee. 2011. Bioinspired polymerization of dopamine to generate melanin-like nanoparticles having an excellent free-radical-scavenging property. *Biomacromolecules* 12 (3):625–32. doi: [10.1021/bm101281b](https://doi.org/10.1021/bm101281b).
- Kaidbey, K. H., P. P. Agin, R. M. Sayre, and A. M. Kligman. 1979. Photoprotection by melanin—a comparison of black and Caucasian skin. *Journal of the American Academy of Dermatology* 1 (3):249–60. doi: [10.1016/S0190-9622\(79\)70018-1](https://doi.org/10.1016/S0190-9622(79)70018-1).
- Kalka, K., H. Mukhtar, A. Turowski-Wanke, and H. Merk. 2000. Biomelanin antioxidants in cosmetics: Assessment based on inhibition of lipid peroxidation. *Skin Pharmacology and Applied Skin Physiology* 13 (3-4):143–9. doi: [10.1159/000029919](https://doi.org/10.1159/000029919).
- Kim, D. J., K.-Y. Ju, and J.-K. Lee. 2012. The synthetic melanin nanoparticles having an excellent binding capacity of heavy metal ions. *Bulletin of the Korean Chemical Society* 33 (11):3788–92. doi: [10.5012/bkcs.2012.33.11.3788](https://doi.org/10.5012/bkcs.2012.33.11.3788).
- Kiran, G. S., A. Dhasayan, A. N. Lipton, J. Selvin, M. V. Arasu, and N. A. Al-Dhabi. 2014. Melanin-templated rapid synthesis of silver nanostructures. *Journal of Nanobiotechnology* 12 (1):18. doi: [10.1186/1477-3155-12-18](https://doi.org/10.1186/1477-3155-12-18).
- Kiran, G. S., S. A. Jackson, S. Priyadharsini, A. D. W. Dobson, and J. Selvin. 2017. Synthesis of Nm-PHB (nanomelanin-polyhydroxy butyrate) nanocomposite film and its protective effect against bio-film-forming multi drug resistant *Staphylococcus aureus*. *Scientific Reports* 7 (1):9167. doi: [10.1038/s41598-017-08816-y](https://doi.org/10.1038/s41598-017-08816-y).
- Kobayashi, N., A. Nakagawa, T. Muramatsu, Y. Yamashina, T. Shirai, M. W. Hashimoto, Y. Ishigaki, T. Ohnishi, and T. Mori. 1998. Supranuclear melanin caps reduce ultraviolet induced DNA photoproducts in human epidermis. *The Journal of Investigative Dermatology* 110 (5):806–10. doi: [10.1046/j.1523-1747.1998.00178.x](https://doi.org/10.1046/j.1523-1747.1998.00178.x).
- Kuang, J., J. L. Guo, and P. B. Messersmith. 2014. High ionic strength formation of DOPA-melanin coating for loading and release of cationic microbial compounds. *Advanced Materials Interfaces* 1 (6): 1400145. doi: [10.1002/admi.201400145](https://doi.org/10.1002/admi.201400145).
- Kumar, C. G., P. Mongolla, S. Pombala, A. Kamle, and J. Joseph. 2011. Physicochemical characterization and antioxidant activity of melanin from a novel strain of *Aspergillus bridgeri* ICTF-201. *Letters in Applied Microbiology* 53 (3):350–8. doi: [10.1111/j.1472-765X.2011.03116.x](https://doi.org/10.1111/j.1472-765X.2011.03116.x).
- Kvam, E., and J. Dahle. 2004. Melanin synthesis may sensitize melanocytes to oxidative DNA damage by ultraviolet A radiation and protect melanocytes from direct DNA damage by ultraviolet B radiation. *Pigment Cell Research* 17 (5):549–50. doi: [10.1111/j.1600-0749.2004.00168.x](https://doi.org/10.1111/j.1600-0749.2004.00168.x).
- Langfelder, K., M. Streibel, B. Jahn, G. Haase, and A. A. Brakhage. 2003. Biosynthesis of fungal melanins and their importance for human pathogenic fungi. *Fungal Genetics and Biology* 38 (2):143–58. doi: [10.1016/S1087-1845\(02\)00526-1](https://doi.org/10.1016/S1087-1845(02)00526-1).
- Latocha, M., E. Chodurek, S. Kurkiewicz, L. Świątkowska, and T. Wilczok. 2000. Pyrolytic GC-MS analysis of melanin from black, gray and yellow strains of *Drosophila melanogaster*. *Journal of Analytical and Applied Pyrolysis* 56 (1):89–98. doi: [10.1016/S0165-2370\(00\)00082-6](https://doi.org/10.1016/S0165-2370(00)00082-6).
- Laxmi, M., N. K. Kurian, S. Smitha, and S. G. Bhat. 2016. Melanin and bacteriocin from marine bacteria inhibit biofilms of foodborne pathogens. *Indian Journal of Biotechnology* 15:392–9.
- Li, W., Z. Wang, M. Xiao, T. Miyoshi, X. Yang, Z. Hu, C. Liu, S. S. C. Chuang, M. D. Shawkey, N. C. Gianneschi, et al. 2019. Mechanism of UVA degradation of synthetic eumelanin. *Biomacromolecules* 20 (12):4593–601. doi: [10.1021/acs.biomac.9b01433](https://doi.org/10.1021/acs.biomac.9b01433).
- Liberti, D., M. L. Alfieri, D. M. Monti, L. Panzella, and A. Napolitano. 2020. A Melanin-related phenolic polymer with potent photoprotective and antioxidant activities for dermo-cosmetic applications. *Antioxidants* 9 (4):270. doi: [10.3390/antiox9040270](https://doi.org/10.3390/antiox9040270).
- Lin, J., M. Wang, H. Hu, X. Yang, B. Wen, Z. Wang, O. Jacobson, J. Song, G. Zhang, G. Niu, et al. 2016. Multimodal-imaging-guided cancer phototherapy by versatile biomimetic theranostics with UV and γ -irradiation protection. *Advanced Materials* 28 (17):3273–9. doi: [10.1002/adma.201505700](https://doi.org/10.1002/adma.201505700).
- Liopo, A., R. Su, and A. A. Oraevsky. 2015. Melanin nanoparticles as a novel contrast agent for optoacoustic tomography. *Photoacoustics* 3 (1):35–43. doi: [10.1016/j.pacs.2015.02.001](https://doi.org/10.1016/j.pacs.2015.02.001).
- Liu, Y., K. Ai, X. Ji, D. Askhatova, R. Du, L. Lu, and J. Shi. 2017. Comprehensive insights into the multi-antioxidative mechanisms of melanin nanoparticles and their application to protect brain from injury in ischemic stroke. *Journal of the American Chemical Society* 139 (2):856–62. doi: [10.1021/jacs.6b11013](https://doi.org/10.1021/jacs.6b11013).
- Liu, Y., K. Ai, J. Liu, M. Deng, Y. He, and L. Lu. 2013. Dopamine-melanin colloidal nanospheres: An efficient near-infrared photothermal therapeutic agent for in vivo cancer therapy. *Advanced Materials (Deerfield Beach, Fla.)* 25 (9):1353–9. doi: [10.1002/adma.201204683](https://doi.org/10.1002/adma.201204683).
- Liu, Y., K. Ai, and L. Lu. 2014. Polydopamine and its derivative materials: Synthesis and promising applications in energy, environmental, and biomedical fields. *Chemical Reviews* 114 (9):5057–115. doi: [10.1021/cr400407a](https://doi.org/10.1021/cr400407a).
- Liu, Y., V. R. Kempf, J. B. Nofsinger, E. E. Weinert, M. Rudnicki, K. Wakamatsu, S. Ito, and J. D. Simon. 2003. Comparison of the structural and physical properties of human hair eumelanin following enzymatic or acid/base extraction. *Pigment Cell Research* 16 (4): 355–65. doi: [10.1034/j.1600-0749.2003.00059.x](https://doi.org/10.1034/j.1600-0749.2003.00059.x).
- Liu, Y., and J. D. Simon. 2003. The effect of preparation procedures on the morphology of melanin from the ink sac of *Sepia officinalis*. *Pigment Cell Research* 16 (1):72–80. doi: [10.1034/j.1600-0749.2003.00009.x](https://doi.org/10.1034/j.1600-0749.2003.00009.x).
- Long, H., D. Del Frari, A. Martin, J. Didierjean, V. Ball, M. Michel, and H. I. E. Ahrach. 2016. Polydopamine as a promising candidate for the design of high performance and corrosion-tolerant polymer electrolyte fuel cell electrodes. *Journal of Power Sources* 307:569–77. doi: [10.1016/j.jpowsour.2015.12.138](https://doi.org/10.1016/j.jpowsour.2015.12.138).
- Longo, D. L., R. Stefania, S. Aime, and A. Oraevsky. 2017. Melanin-based contrast agents for biomedical optoacoustic imaging and theranostic applications. *International Journal of Molecular Sciences* 18 (8):1719. doi: [10.3390/ijms18081719](https://doi.org/10.3390/ijms18081719).
- Longo, D. L., R. Stefania, C. Callari, F. De Rose, R. Rolle, L. Conti, L. Consolino, F. Arena, and S. Aime. 2017. Water soluble melanin derivatives for dynamic contrast enhanced photoacoustic imaging of tumor vasculature and response to antiangiogenic therapy. *Advanced Healthcare Materials* 6 (1):1600550. doi: [10.1002/adhm.201600550](https://doi.org/10.1002/adhm.201600550).
- Lopusiewicz, Ł., E. Drożłowska, P. Trocer, M. Kosteł, M. Śliwiński, M. H. F. Henriques, A. Bartkowiak, and P. Sobolewski. 2020. Whey protein concentrate/isolate biofunctional films modified with melanin from watermelon (*Citrullus lanatus*) seeds. *Materials* 13 (17): 3876. doi: [10.3390/ma13173876](https://doi.org/10.3390/ma13173876).
- Lopusiewicz, Ł., F. Jedra, and M. Mizielńska. 2018a. New polylactic acid active packaging composite films incorporated with fungal melanin. *Polymers* 10 (4):386. doi: [10.3390/polym10040386](https://doi.org/10.3390/polym10040386).
- Lopusiewicz, Ł., F. Jedra, and M. Mizielńska. 2018b. The application of melanin modified gelatin coatings for packaging and the oxidative stability of pork lard. *World Scientific News* 101:108–19.
- Lopusiewicz, Ł., F. Jedra, and M. Mizielńska. 2018c. New active packaging films made from gelatin modified with fungal melanin. *World Scientific News* 101:1–30.
- Lynge, M. E., R. van der Westen, A. Postma, and B. Städler. 2011. Polydopamine—a nature-inspired polymer coating for biomedical science. *Nanoscale* 3 (12):4916–28. doi: [10.1039/c1nr10969c](https://doi.org/10.1039/c1nr10969c).
- Madhusudhan, D. N., D. Agsar, and M. B. Sulochana. 2015. Water soluble melanin of *Streptomyces lusitanus* DMZ3 persuade synthesis of enhanced bio-medically active silver nanoparticles. *Journal of Cluster Science* 26 (4):1077–89. doi: [10.1007/s10876-014-0798-x](https://doi.org/10.1007/s10876-014-0798-x).
- Maher, S., M. Mahmoud, M. Rizk, and H. Kalil. 2019. Synthetic melanin nanoparticles as peroxynitrite scavengers, photothermal anti-cancer and heavy metals removal platforms. *Environmental Science and Pollution Research* 27 (16):19115–26. doi: [10.1007/s11356-019-05111-3](https://doi.org/10.1007/s11356-019-05111-3).
- Marks, M. S., and M. C. Seabra. 2001. The melanosome: Membrane dynamics in black and white. *Nature Reviews. Molecular Cell Biology* 2 (10):738–48. doi: [10.1038/35096009](https://doi.org/10.1038/35096009).

- Marrot, L., J. P. Belaidi, J. R. Meunier, P. Perez, and C. Agapakis-Causse. 1999. The human melanocyte as a particular target for UVA radiation and an endpoint for photoprotection assessment. *Photochemistry and Photobiology* 69 (6):686–93. doi: [10.1111/j.1751-1097.1999.tb03347.x](https://doi.org/10.1111/j.1751-1097.1999.tb03347.x).
- Menter, J. M. 2016. Melanin from a physicochemical point of view. *Polymer International* 65 (11):1300–5. doi: [10.1002/pi.5194](https://doi.org/10.1002/pi.5194).
- Meredith, P., and T. Sarna. 2006. The physical and chemical properties of eumelanin. *Pigment Cell Research* 19 (6):572–94. doi: [10.1111/j.1600-0749.2006.00345.x](https://doi.org/10.1111/j.1600-0749.2006.00345.x).
- Montefiori, D. C., A. Modliszewski, D. I. Shaff, and J. Zhou. 1990. Inhibition of human immunodeficiency virus type 1 replication and cytopathicity by synthetic soluble catecholamine melanins in vitro. *Biochemical and Biophysical Research Communications* 168 (1): 200–5. doi: [10.1016/0006-291X\(90\)91694-N](https://doi.org/10.1016/0006-291X(90)91694-N).
- Montefiori, D. C., and J. Y. Zhou. 1991. Selective antiviral activity of synthetic soluble L-tyrosine and L-dopa melanins against human immunodeficiency virus in vitro. *Antiviral Research* 15 (1):11–25. doi: [10.1016/0166-3542\(91\)90037-r](https://doi.org/10.1016/0166-3542(91)90037-r).
- Moreiras, H., M. Lopes-da-Silva, M. C. Seabra, and D. C. Barral. 2019. Melanin processing by keratinocytes: A non-microbial type of host-pathogen interaction? *Traffic* 20 (4):301–4. doi: [10.1111/tra.12638](https://doi.org/10.1111/tra.12638).
- Mrówczyński, R., A. Bunge, and J. Liebscher. 2014. Polydopamine-An organocatalyst rather than an innocent polymer. *Chemistry* 20 (28): 8647–53. doi: [10.1002/chem.201402532](https://doi.org/10.1002/chem.201402532).
- Nicolaus, B. J. R. 2005. A critical review of the function of neuromelanin and an attempt to provide a unified theory. *Medical Hypotheses* 65 (4):791–6. doi: [10.1016/j.mehy.2005.04.011](https://doi.org/10.1016/j.mehy.2005.04.011).
- Nicolaus, R. A., M. Piattelli, and E. Fattorusso. 1964. The structure of melanins and melanogenesis. IV. On some natural melanins. *Tetrahedron* 20 (5):1163–72. doi: [10.1016/s0040-4020\(01\)98983-5](https://doi.org/10.1016/s0040-4020(01)98983-5).
- Noonan, F. P., M. R. Zaidi, A. Wolnicka-Glubisz, M. R. Anver, J. Bahi, A. Wielgus, J. Cadet, T. Douki, S. Mouret, M. A. Tucker, et al. 2012. Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. *Nature Communications* 3: 884. doi: [10.1038/ncomms1893](https://doi.org/10.1038/ncomms1893).
- Nosanchuk, J. D., and A. Casadevall. 2006. Impact of melanin on microbial virulence and clinical resistance to antimicrobial compounds. *Antimicrobial Agents and Chemotherapy* 50 (11):3519–28. doi: [10.1128/AAC.00545-06](https://doi.org/10.1128/AAC.00545-06).
- Nosanchuk, J. D., R. E. Stark, and A. Casadevall. 2015. Fungal melanin: What do we know about structure? *Frontiers in Microbiology* 6: 1463–7. doi: [10.3389/fmicb.2015.01463](https://doi.org/10.3389/fmicb.2015.01463).
- Paim, S., L. F. Linhares, A. S. Mangrich, and J. P. Martin. 1990. Characterization of fungal melanins and soil humic acids by chemical analysis and infrared spectroscopy. *Biology & Fertility of Soils* 10:72–6.
- Perring, J., F. Crawshaw-Williams, C. Huang, and H. E. Townley. 2018. Bio-inspired melanin nanoparticles induce cancer cell death by iron adsorption. *Journal of Materials Science. Materials in Medicine* 29 (12):181. doi: [10.1007/S10856-018-6190-X](https://doi.org/10.1007/S10856-018-6190-X).
- Plonka, P. M., and M. Grabacka. 2006. Melanin synthesis in microorganisms – Biotechnological and medical aspects. *Acta Biochimica Polonica* 53 (3):429–43.
- Prală, I.-E., R.-C. Moldovan, A.-M. Petracă, M. Ilieş, S.-C. Hegheş, I. Ielciu, R. Nicoară, M. Moldovan, M. Ene, M. Radu, et al. 2019. From extraction to advanced analytical methods: The challenges of melanin analysis. *International Journal of Molecular Sciences* 20 (16): 3943. doi: [10.3390/ijms20163943](https://doi.org/10.3390/ijms20163943).
- Pyo, J., K.-Y. Ju, and J.-K. Lee. 2016. Artificial pheomelanin nanoparticles and their photo-sensitization properties. *Journal of Photochemistry and Photobiology. B, Biology* 160:330–5. doi: [10.1016/j.jphotobiol.2016.04.022](https://doi.org/10.1016/j.jphotobiol.2016.04.022).
- Qi, C., L. H. Fu, H. Xu, T. F. Wang, J. Lin, and P. Huang. 2019. Melanin/polydopamine-based nanomaterials for biomedical applications. *Science China Chemistry* 62 (2):162–88. doi: [10.1007/s11426-018-9392-6](https://doi.org/10.1007/s11426-018-9392-6).
- Rai, M., A. P. Ingle, I. Gupta, R. Pandit, P. Paralikar, A. Gade, M. V. Chaud, and C. A. dos Santos. 2019. Smart nanopackaging for the enhancement of food shelf life. *Environmental Chemistry Letters* 17 (1):277–90. doi: [10.1007/s10311-018-0794-8](https://doi.org/10.1007/s10311-018-0794-8).
- Raposo, G., and M. S. Marks. 2007. Melanosomes-dark organelles enlighten endosomal membrane transport. *Nature Reviews. Molecular Cell Biology* 8 (10):786–97. doi: [10.1038/nrm2258](https://doi.org/10.1038/nrm2258).
- Roy, S., H. C. Kim, J. W. Kim, L. Zhai, Q. Y. Zhu, and J. Kim. 2020. Incorporation of melanin nanoparticles improves UV-shielding, mechanical and antioxidant properties of cellulose nanofiber based nanocomposite films. *Materials Today Communications* 24:100984. doi: [10.1016/j.mtcomm.2020.100984](https://doi.org/10.1016/j.mtcomm.2020.100984).
- Roy, S., H.-J. Kim, and J.-W. Rhim. 2021. Synthesis of carboxymethyl cellulose and agar-based multifunctional films reinforced with cellulose nanocrystals and shikonin. *ACS Applied Polymer Materials*. doi: [10.1021/acsapm.0c01307](https://doi.org/10.1021/acsapm.0c01307).
- Roy, S., and J. W. Rhim. 2019a. Melanin-mediated synthesis of copper oxide nanoparticles and preparation of functional agar/CuO NP nanocomposite films. *Journal of Nanomaterials* 2019:1–10. doi: [10.1155/2019/2840517](https://doi.org/10.1155/2019/2840517).
- Roy, S., and J. W. Rhim. 2019b. Agar-based antioxidant composite films incorporated with melanin nanoparticles. *Food Hydrocolloids* 94:391–8. doi: [10.1016/j.foodhyd.2019.03.038](https://doi.org/10.1016/j.foodhyd.2019.03.038).
- Roy, S., and J. W. Rhim. 2019c. Carrageenan-based antimicrobial bionanocomposite films incorporated with ZnO nanoparticles stabilized by melanin. *Food Hydrocolloids* 90:500–7. doi: [10.1016/j.foodhyd.2018.12.056](https://doi.org/10.1016/j.foodhyd.2018.12.056).
- Roy, S., and J. W. Rhim. 2019d. Preparation of carrageenan-based functional nanocomposite films incorporated with melanin nanoparticles. *Colloids and Surfaces. B, Biointerfaces* 176:317–24. doi: [10.1016/j.colsurfb.2019.01.023](https://doi.org/10.1016/j.colsurfb.2019.01.023).
- Roy, S., and J.-W. Rhim. 2020a. Anthocyanin food colorant and its application in pH-responsive color change indicator films. *Critical Reviews in Food Science and Nutrition*. doi: [10.1080/10408398.2020.1776211](https://doi.org/10.1080/10408398.2020.1776211).
- Roy, S., and J.-W. Rhim. 2020b. Preparation of bioactive functional poly(lactic acid)/curcumin composite film for food packaging application. *International Journal of Biological Macromolecules* 162: 1780–9. doi: [10.1016/j.ijbiomac.2020.08.094](https://doi.org/10.1016/j.ijbiomac.2020.08.094).
- Roy, S., S. Shankar, and J. W. Rhim. 2019. Melanin-mediated synthesis of silver nanoparticle and its use for the preparation of carrageenan-based antibacterial films. *Food Hydrocolloids* 88:237–46. doi: [10.1016/j.foodhyd.2018.10.013](https://doi.org/10.1016/j.foodhyd.2018.10.013).
- Roy, S., L. Van Hai, H. C. Kim, L. Zhai, and J. Kim. (2020). Preparation and characterization of synthetic melanin-like nanoparticles reinforced chitosan nanocomposite films. *Carbohydrate Polymers* 231:115729. doi: [10.1016/j.carbpol.2019.115729](https://doi.org/10.1016/j.carbpol.2019.115729).
- Różańska, M., T. Sarna, E. J. Land, and T. G. Truscott. 1999. Free radical scavenging properties of melanin: Interaction of eu- and pyo-melanin models with reducing and oxidising radicals. *Free Radical Biology and Medicine* 26 (5-6):518–25. doi: [10.1016/S0891-5849\(98\)00234-2](https://doi.org/10.1016/S0891-5849(98)00234-2).
- Sava, V. M., B. N. Galkin, M.-Y. Hong, P.-C. Yang, and G. S. Huang. 2001. A novel melanin-like pigment derived from black tea leaves with immuno-stimulating activity. *Food Research International* 34 (4):337–43. doi: [10.1016/S0963-9969\(00\)00173-3](https://doi.org/10.1016/S0963-9969(00)00173-3).
- Sava, V. M., Y. Hung, V. Blagodarsky, M.-Y. Hong, and G. Huang. 2003. The liver-protecting activity of melanin-like pigment derived from black tea. *Food Research International* 36 (5):505–11. doi: [10.1016/S0963-9969\(02\)00199-0](https://doi.org/10.1016/S0963-9969(02)00199-0).
- Schindler, M., H. Sawada, K. Tietjen, T. Hamada, H. Hagiwara, and S. Banaba. 2019. Melanin synthesis in the cell wall. In *Modern crop protection compounds*, eds P. Jeschke, M. Witschel, W. Krämer and U. Schirmer. 879–909. Weinheim, Germany: Wiley. doi: [10.1002/9783527699261.ch22](https://doi.org/10.1002/9783527699261.ch22).
- Schweitzer, A. D., E. Revskaya, P. Chu, V. Pazo, M. Friedman, J. D. Nosanchuk, S. Cahill, S. Frases, A. Casadevall, and E. Dadachova. 2010. Melanin-covered nanoparticles for protection of bone marrow during radiation therapy of cancer. *International Journal of Radiation Oncology, Biology, Physics* 78 (5):1494–502. doi: [10.1016/j.ijrobp.2010.02.020](https://doi.org/10.1016/j.ijrobp.2010.02.020).

- Selvakumar, P., S. Rajasekar, K. Periasamy, and N. Raaman. 2008. Isolation and characterization of melanin pigment from *Pleurotus cystidiosus* (telomorph of *Antromycopsis macrocarpa*). *World Journal of Microbiology and Biotechnology* 24 (10):2125–31. doi: [10.1007/s11274-008-9718-2](https://doi.org/10.1007/s11274-008-9718-2).
- Shankar, S., Y. J. Bang, and J. W. Rhim. 2019. Antibacterial LDPE/GSE/Mel/ZnONP composite film-coated wrapping paper for convenience food packaging application. *Food Packaging and Shelf Life* 22:100421. doi: [10.1016/j.fpsl.2019.100421](https://doi.org/10.1016/j.fpsl.2019.100421).
- Shankar, S., L.-F. Wang, and J.-W. Rhim. 2019. Effect of melanin nanoparticles on the mechanical, water vapor barrier, and antioxidant properties of gelatin-based films for food packaging application. *Food Packaging and Shelf Life* 21:100363. doi: [10.1016/j.fpsl.2019.100363](https://doi.org/10.1016/j.fpsl.2019.100363).
- Shanmuganathan, K., J. H. Cho, P. Iyer, S. Baranowitz, and C. J. Ellison. 2011. Thermooxidative stabilization of polymers using natural and synthetic melanins. *Macromolecules* 44 (24):9499–507. doi: [10.1021/ma202170n](https://doi.org/10.1021/ma202170n).
- Sharma, S., S. Barkauskaite, A. K. Jaiswal, and S. Jaiswal. 2021. Essential oils as additives in active food packaging. *Food Chemistry* 343:128403. doi: [10.1016/j.foodchem.2020.128403](https://doi.org/10.1016/j.foodchem.2020.128403).
- Shi, Y., D. Xu, M. Liu, L. Fu, Q. Wan, L. Mao, Y. Dai, Y. Wen, X. Zhang, and Y. Wei. 2018. Room temperature preparation of fluorescent starch nanoparticles from starch-dopamine conjugates and their biological applications. *Materials Science & Engineering C, Materials for Biological Applications* 82:204–9. doi: [10.1016/j.msec.2017.08.070](https://doi.org/10.1016/j.msec.2017.08.070).
- Shinkichi, H., Y. Takekoshi, and Y. Arai. 1993. Cosmetics based on naturally derived melanin-coated pigments. US Patent (US5380359 A). <https://patents.google.com/patent/US5380359A/en>.
- Si, J., and H. Yang. 2011. Preparation and characterization of bio-compatible Fe₃O₄@Polydopamine spheres with core/shell nanostructure. *Materials Chemistry and Physics* 128 (3):519–24. doi: [10.1016/j.matchemphys.2011.03.039](https://doi.org/10.1016/j.matchemphys.2011.03.039).
- Sidibe, S., F. Saal, A. Rhodes-Feuillette, S. Lagaye, L. Pelicano, M. Canivet, J. Peries, and L. Dianoux. 1996. Effects of serotonin and melanin on in vitro HIV-1 infection. *Journal of Biological Regulators and Homeostatic Agents* 10 (1):19–24.
- Simonovic, B., V. Vucelic, A. Hadzi-Pavlovic, K. Stepien, T. Wilczok, and D. Vucelic. 1990. Thermogravimetry and differential scanning calorimetry of natural and synthetic melanins. *Journal of Thermal Analysis and Analysis* 36 (7-8):2475–82. doi: [10.1007/BF01913644](https://doi.org/10.1007/BF01913644).
- Solano, F. 2014. Melanins: Skin pigments and much more – Types, structural models, biological functions, and formation routes. *New Journal of Science* 2014:1–28. doi: [10.1155/2014/498276](https://doi.org/10.1155/2014/498276).
- Solano, F. 2016. Photoprotection versus photodamage: Updating an old but still unsolved controversy about melanin. *Polymer International* 65 (11):1276–87. doi: [10.1002/pi.5117](https://doi.org/10.1002/pi.5117).
- Solano, F. 2017. Melanin and melanin-related polymers as materials with biomedical and biotechnological applications-cuttlefish ink and mussel foot proteins as inspired biomolecules. *International Journal of Molecular Sciences* 18 (7):1561. doi: [10.3390/ijms18071561](https://doi.org/10.3390/ijms18071561).
- Solano, F. 2020. Photoprotection and skin pigmentation: Melanin-related molecules and some other new agents obtained from natural sources. *Molecules* 25 (7):1537. doi: [10.3390/molecules25071537](https://doi.org/10.3390/molecules25071537).
- Tarangini, K., and S. Mishra. 2014. Production of melanin by soil microbial isolate on fruit waste extract: Two step optimization of key parameters. *Biotechnology Reports* 4:139–46. doi: [10.1016/j.btre.2014.10.001](https://doi.org/10.1016/j.btre.2014.10.001).
- Tolleson, W. H. 2005. Human melanocyte biology, toxicology, and pathology. *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews* 23 (2): 105–61. doi: [10.1080/10590500500234970](https://doi.org/10.1080/10590500500234970).
- Tran-Ly, A. N., C. Reyes, F. W. Schwarze, and J. Ribera. 2020. Microbial production of melanin and its various applications. *World Journal of Microbiology and Biotechnology* 36 (11):1–9. doi: [10.1007/s11274-020-02941-z](https://doi.org/10.1007/s11274-020-02941-z).
- Tu, Y., Y. Sun, Y. Tian, M. Xie, and J. Chen. 2009. Physicochemical characterization and antioxidant activity of melanin from the muscles of Taihe Black-bone silky fowl (*Gallus gallus domesticus* Brisson). *Food Chemistry* 114 (4):1345–50. doi: [10.1016/j.foodchem.2008.11.015](https://doi.org/10.1016/j.foodchem.2008.11.015).
- Vasantha Bharathi, V., R. Lakshminarayanan, and S. Jayalakshmi. 2011. Melanin production from marine *Streptomyces*. *African Journal of Biotechnology* 10 (54):11224–34. doi: [10.5897/AJB11.296](https://doi.org/10.5897/AJB11.296).
- Varga, M., O. Berkesi, Z. Darula, N. V. May, and A. Palágyi. 2016. Structural characterization of allomelanin from black oat. *Phytochemistry* 130:313–20. doi: [10.1016/j.phytochem.2016.07.002](https://doi.org/10.1016/j.phytochem.2016.07.002).
- Vilela, C., M. Kurek, Z. Hayouka, B. Röcker, S. Yildirim, M. D. C. Antunes, J. Nilsen-Nygaard, M. K. Pettersen, and C. S. R. Freire. 2018. A concise guide to active agents for active food packaging. *Trends in Food Science & Technology* 80:212–22. doi: [10.1016/j.tifs.2018.08.006](https://doi.org/10.1016/j.tifs.2018.08.006).
- Vitiello, G., A. Pezzella, A. Zanfardino, B. Silvestri, P. Giudicianni, A. Costantini, M. Varcamonti, F. Branda, and G. Luciani. 2017. Antimicrobial activity of eumelanin-based hybrids: The role of TiO₂ in modulating the structure and biological performance. *Materials Science & Engineering C, Materials for Biological Applications* 75: 454–62. doi: [10.1016/j.msec.2016.12.135](https://doi.org/10.1016/j.msec.2016.12.135).
- Wang, H., Y. Pan, X. Tang, and Z. Huang. 2006. Isolation and characterization of melanin from *Osmanthus fragrans*' seeds. *LWT - Food Science and Technology* 39 (5):496–502. doi: [10.1016/j.lwt.2005.04.001](https://doi.org/10.1016/j.lwt.2005.04.001).
- Wang, K., Y. Hou, B. Poudel, D. Yang, Y. Jiang, M. -G. Kang, K. Wang, C. Wu, and S. Priya. 2019. Melanin-perovskite composites for photothermal conversion. *Advanced Energy Materials* 9 (37): 1901753. doi: [10.1002/aenm.201901753](https://doi.org/10.1002/aenm.201901753).
- Wang, L.-F., and J.-W. Rhim. 2019. Isolation and characterization of melanin from black garlic and sepio ink. *LWT* 99:17–23. doi: [10.1016/j.lwt.2018.09.033](https://doi.org/10.1016/j.lwt.2018.09.033).
- Wang, Q., R. Zhang, M. Lu, G. You, Y. Wang, G. Chen, C. Zhao, Z. Wang, X. Song, Y. Wu, et al. 2017. Bioinspired polydopamine-coated hemoglobin as potential oxygen carrier with antioxidant properties. *Biomacromolecules* 18 (4):1333–41. doi: [10.1021/acs.biomac.7b00077](https://doi.org/10.1021/acs.biomac.7b00077).
- Wang, X., J. Sheng, and M. Yang. 2019. Melanin-based nanoparticles in biomedical applications: From molecular imaging to treatment of diseases. *Chinese Chemical Letters* 30 (3):533–40. doi: [10.1016/j.cclet.2018.10.010](https://doi.org/10.1016/j.cclet.2018.10.010).
- Wang, X., S. Zhou, and L. Wu. 2014. Fabrication of Fe³⁺ doped Mg/Al layered double hydroxides and their application in UV light-shielding coatings. *Journal of Materials Chemistry C* 2 (29):5752–8. doi: [10.1039/c4tc00437j](https://doi.org/10.1039/c4tc00437j).
- Wang, Y., T. Li, P. Ma, H. Bai, Y. Xie, M. Chen, and W. Dong. 2016. Simultaneous enhancements of UV-shielding properties and photo-stability of poly(vinyl alcohol) via incorporation of sepio eumelanin. *ACS Sustainable Chemistry & Engineering* 4 (4):2252–8. doi: [10.1021/acssuschemeng.5b01734](https://doi.org/10.1021/acssuschemeng.5b01734).
- Wang, Y., T. Li, X. Wang, P. Ma, H. Bai, W. Dong, Y. Xie, and M. Chen. 2016. Superior performance of polyurethane based on natural melanin nanoparticles. *Biomacromolecules* 17 (11):3782–9. doi: [10.1021/acs.biomac.6b01298](https://doi.org/10.1021/acs.biomac.6b01298).
- Wang, Y., J. Su, T. Li, P. Ma, H. Bai, Y. Xie, M. Chen, and W. Dong. 2017. A novel UV-shielding and transparent polymer film: When bioinspired dopamine-melanin hollow nanoparticles join polymers. *ACS Applied Materials & Interfaces* 9 (41):36281–9. doi: [10.1021/acsami.7b08763](https://doi.org/10.1021/acsami.7b08763).
- Wang, Y., X. Wang, T. Li, P. Ma, S. Zhang, M. Du, W. Dong, Y. Xie, and M. Chen. 2018. Effects of melanin on optical behavior of polymer: From natural pigment to materials applications. *ACS Applied Materials & Interfaces* 10 (15):13100–6. doi: [10.1021/acsami.8b02658](https://doi.org/10.1021/acsami.8b02658).
- Wang, Y., Z. Wang, P. Ma, H. Bai, W. Dong, Y. Xie, and M. Chen. 2015. Strong nanocomposite reinforcement effects in poly(vinyl alcohol) with melanin nanoparticles. *RSC Advances* 5 (89):72691–8. doi: [10.1039/C5RA1233J](https://doi.org/10.1039/C5RA1233J).
- Xie, W., E. Pakdel, Y. Liang, Y. J. Kim, D. Liu, L. Sun, and X. Wang. 2019. Natural eumelanin and its derivatives as multifunctional materials for bioinspired applications: A review. *Biomacromolecules* 20 (12):4312–31. doi: [10.1021/acs.biomac.9b01413](https://doi.org/10.1021/acs.biomac.9b01413).

- Xin, C., J. H. Ma, C. J. Tan, Z. Yang, F. Ye, C. Long, S. Ye, and D. B. Hou. 2015. Preparation of melanin from *Cathartes molossus* L. and preliminary study on its chemical structure. *Journal of Bioscience and Bioengineering* 119 (4):446–54. doi: [10.1016/j.jbiosc.2014.09.009](https://doi.org/10.1016/j.jbiosc.2014.09.009).
- Xing, Q., P. Buono, D. Ruch, P. Dubois, L. Wu, and W. J. Wang. 2019. Biodegradable UV-blocking films through core-shell lignin-melanin nanoparticles in poly(butylene adipate-co-terephthalate). *ACS Sustainable Chemistry & Engineering* 7 (4):4147–57. doi: [10.1021/acssuschemeng.8b05755](https://doi.org/10.1021/acssuschemeng.8b05755).
- Xu, C., J. Li, L. Yang, F. Shi, L. Yang, and M. Ye. 2017. Antibacterial activity and a membrane damage mechanism of Lachnum YM30 melanin against *Vibrio parahaemolyticus* and *Staphylococcus aureus*. *Food Control* 73:1445–51. doi: [10.1016/j.foodcont.2016.10.048](https://doi.org/10.1016/j.foodcont.2016.10.048).
- Xu, R., A. Gouda, M. F. Caso, F. Soavi, and C. Santato. 2019. Melanin: A greener route to enhance energy storage under solar light. *ACS Omega* 4 (7):12244–51. doi: [10.1021/acsomega.9b01039](https://doi.org/10.1021/acsomega.9b01039).
- Yamaguchi, Y., K. Takahashi, B. Z. Zmudzka, A. Kornhauser, S. A. Miller, T. Tadokoro, W. Berens, J. Z. Beer, and V. J. Hearing. 2006. Human skin responses to UV radiation: Pigment in the upper epidermis protects against DNA damage in the lower epidermis and facilitates apoptosis. *FASEB Journal* 20 (9):1486–8. doi: [10.1096/fj.06-5725fje](https://doi.org/10.1096/fj.06-5725fje).
- Yan, J., Y. Ji, P. Zhang, X. Lu, Q. Fan, D. Pan, R. Yang, Y. Xu, L. Wang, L. Zhang, et al. 2016. Melanin nanoparticles as an endogenous agent for efficient iron overload therapy. *Journal of Materials Chemistry. B* 4 (45):7233–40. doi: [10.1039/c6tb01558a](https://doi.org/10.1039/c6tb01558a).
- Yang, M., L. Li, S. Yu, J. Liu, and J. Shi. 2020. High performance of alginate/polyvinyl alcohol composite film based on natural original melanin nanoparticles used as food thermal insulating and UV-vis block. *Carbohydrate Polymers* 233:115884. doi: [10.1016/j.carbpol.2020.115884](https://doi.org/10.1016/j.carbpol.2020.115884).
- Ye, M., G. Y. Guo, Y. Lu, S. Song, H. Y. Wang, and L. Yang. 2014. Purification, structure and anti-radiation activity of melanin from Lachnum YM404. *International Journal of Biological Macromolecules* 63:170–6. doi: [10.1016/j.ijbiomac.2013.10.046](https://doi.org/10.1016/j.ijbiomac.2013.10.046).
- Ye, Z., Y. Lu, S. Zong, L. Yang, F. Shaikh, J. Li, and M. Ye. 2019. Structure, molecular modification and anti-tumor activity of melanin from *Lachnum singnerianum*. *Process Biochemistry* 76:203–12. doi: [10.1016/j.procbio.2018.09.007](https://doi.org/10.1016/j.procbio.2018.09.007).
- Yerger, V. B., and R. E. Malone. 2006. Melanin and nicotine: A review of the literature. *Nicotine & Tobacco Research* 8 (4):487–98. doi: [10.1080/14622200600790039](https://doi.org/10.1080/14622200600790039).
- Yong, H., and J. Liu. 2020. Recent advances in the preparation, physical and functional properties, and applications of anthocyanins-based active and intelligent packaging films. *Food Packaging and Shelf Life* 26:100550. doi: [10.1016/j.fpsl.2020.100550](https://doi.org/10.1016/j.fpsl.2020.100550).
- Zerrad, A., J. Anissi, J. Ghanam, K. Sendide, and M. E. L. Hassouni. 2014. Antioxidant and antimicrobial activities of melanin produced by a *Pseudomonas balearica* strain. *Journal of Biotechnology Letters* 5 (1):87–94.
- Zhang, C., X. Zhao, S. Guo, T. Lin, and H. Guo. 2017. Highly effective photothermal chemotherapy with pH-responsive polymer-coated drug-loaded melanin-like nanoparticles. *International Journal of Nanomedicine* 12:1827–40. doi: [10.2147/IJN.S130539](https://doi.org/10.2147/IJN.S130539).
- Zhang, R., Q. Fan, M. Yang, K. Cheng, X. Lu, L. Zhang, W. Huang, and Z. Cheng. 2015. Engineering melanin nanoparticles as an efficient drug-delivery system for imaging-guided chemotherapy. *Advanced Materials* 27 (34):5063–9. doi: [10.1002/adma.201502201](https://doi.org/10.1002/adma.201502201).
- Zhang, X., X. Nan, W. Shi, Y. Sun, H. Su, Y. He, X. Liu, Z. Zhang, and D. Ge. 2017. Polydopamine-functionalized nanographene oxide: A versatile nanocarrier for chemotherapy and photothermal therapy. *Nanotechnology* 28 (29):295102. doi: [10.1088/1361-6528/aa761b](https://doi.org/10.1088/1361-6528/aa761b).
- Zhang, X., S. Wang, L. Xu, L. Feng, Y. Ji, L. Tao, S. Li, and Y. Wei. 2012. Biocompatible polydopamine fluorescent organic nanoparticles: Facile preparation and cell imaging. *Nanoscale* 4 (18):5581–4. doi: [10.1039/c2nr31281f](https://doi.org/10.1039/c2nr31281f).
- Zhao, P., J. Li, Y. Wang, and H. Jiang. 2007. Broad-spectrum antimicrobial activity of the reactive compounds generated in vitro by *Manduca sexta* phenoloxidase. *Insect Biochemistry and Molecular Biology* 37 (9):952–9. doi: [10.1016/j.ibmb.2007.05.001](https://doi.org/10.1016/j.ibmb.2007.05.001).
- Zherebin, Y. L., S. Y. Makan, V. M. Sava, and A. V. Bogatsky. 1982. Process producing of water-soluble melanin. SU Patent 939446.
- Zhong, G., X. Yang, X. Jiang, A. Kumar, H. Long, J. Xie, L. Zheng, and J. Zhao. 2019. Dopamine-melanin nanoparticles scavenge reactive oxygen and nitrogen species and activate autophagy for osteoarthritis therapy. *Nanoscale* 11 (24):11605–16. doi: [10.1039/c9nr03060c](https://doi.org/10.1039/c9nr03060c).
- Zhong, X., K. Yang, Z. Dong, X. Yi, Y. Wang, C. Ge, Y. Zhao, and Z. Liu. 2015. Polydopamine as a biocompatible multifunctional nanocarrier for combined radioisotope therapy and chemotherapy of cancer. *Advanced Functional Materials* 25 (47):7327–36. doi: [10.1002/adfm.201503587](https://doi.org/10.1002/adfm.201503587).
- Zhou, J., C. Wang, P. Wang, P. B. Messersmith, and H. Duan. 2015. Multifunctional magnetic nanochains: Exploiting self-polymerization and versatile reactivity of mussel-inspired polydopamine. *Chemistry of Materials* 27 (8):3071–6. doi: [10.1021/acs.chemmater.5b00524](https://doi.org/10.1021/acs.chemmater.5b00524).
- Zhu, H., C. C. He, and Q. H. Chu. 2011. Inhibition of quorum sensing in *Chromobacterium violaceum* by pigments extracted from *Auricularia auricula*. *Letters in Applied Microbiology* 52 (3):269–74. doi: [10.1111/j.1472-765X.2010.02993.x](https://doi.org/10.1111/j.1472-765X.2010.02993.x).
- Zonios, G., A. Dimou, I. Bassukas, D. Galaris, A. Tsolakidis, and E. Kaxiras. 2008. Melanin absorption spectroscopy: New method for noninvasive skin investigation and melanoma detection. *Journal of Biomedical Optics* 13 (1):014017. doi: [10.1117/1.2844710](https://doi.org/10.1117/1.2844710).
- Zou, Y., Y. Zhao, and W. Hu. 2015. Chemical composition and radical scavenging activity of melanin from *Auricularia auricula* fruiting bodies. *Food Science and Technology (Campinas)* 35 (2):253–8. doi: [10.1590/1678-457X.6482](https://doi.org/10.1590/1678-457X.6482).