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MELASMA: ADVANCES IN PATHOPHYSIOLOGY AND INNOVATIVE THERAPEUTIC STRATEGIES BASED ON NATURAL BIOACTIVES AND NANOTECHNOLOGY[1]

MELASMA: AVANÇOS NA FISIOPATOLOGIA E ESTRATÉGIAS TERAPÊUTICAS INOVADORAS BASEADAS EM BIOATIVOS NATURAIS E NANOTECNOLOGIA

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ABSTRACT

Melasma is a chronic and multifactorial pigmentary disorder characterized by recurrent skin hyperpigmentation, strongly associated with oxidative stress, inflammation, and melanocytic hyperactivity induced mainly by ultraviolet radiation, genetic predisposition, and hormonal alterations. Despite available conventional therapies, high recurrence rates and adverse effects highlight the need for safer and more innovative approaches. This study aimed to analyze advances in the pathophysiological understanding of melasma, discuss limitations of current therapies, evaluate the potential of natural bioactive compounds as antioxidant and depigmenting agents, and examine the applicability of nanostructured systems to optimize cutaneous delivery. A narrative literature review was conducted using PubMed and Scopus databases, including original articles without temporal restriction. Thematic analysis showed that oxidative stress and inflammation play central roles in maintaining hyperpigmentation, while flavonoids and other phenolic compounds demonstrate melanogenesis-modulating potential. In addition, nanostructured systems have shown promise in improving the stability, bioavailability, and therapeutic efficacy of these bioactives. In conclusion, the integration of natural bioactives and nanotechnology represents an innovative and pathophysiologically grounded strategy for melasma management.

Keywords: Antioxidants; Bioactive compounds; Hyperpigmentation; Nanocarriers.

RESUMO

O melasma é uma disfunção pigmentária crônica e multifatorial, caracterizada por hiperpigmentação cutânea recorrente, fortemente associada ao estresse oxidativo, à inflamação e à hiperatividade melanocítica induzida principalmente pela radiação ultravioleta, predisposição genética e alterações hormonais. Apesar das terapias convencionais disponíveis, as altas taxas de recidiva e os efeitos adversos evidenciam a necessidade de abordagens mais seguras e inovadoras. Este estudo teve como objetivo analisar os avanços na compreensão fisiopatológica do melasma, discutir as limitações das terapias atuais, avaliar o potencial de compostos bioativos naturais como agentes antioxidantes e despigmentantes e examinar a aplicabilidade de sistemas nanoestruturados na otimização da entrega cutânea. Trata-se de uma revisão narrativa da literatura, realizada nas bases PubMed e Scopus, incluindo artigos originais sem recorte temporal. A análise temática demonstrou que o estresse oxidativo e a inflamação desempenham papel central na manutenção da hiperpigmentação, enquanto flavonoides e outros compostos fenólicos apresentam potencial modulador da melanogênese. Além disso, sistemas nanoestruturados mostraram-se promissores ao aumentar a estabilidade,

1 Narrative review article.

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a biodisponibilidade e a eficácia terapêutica desses bioativos. Conclui-se que a integração entre bioativos naturais e nanotecnologia representa uma estratégia inovadora e fisiopatologicamente fundamentada para o manejo do melasma.Parte inferior do formulário.

Palavras-chave: *Antioxidante; Compostos bioativos; Hiperpigmentação; Nanocarreadores.*

1 INTRODUCTION

Melasma is an acquired and chronic hyperpigmentation disorder that mainly affects photoexposed areas, especially the face (Ocampo-Candiani *et al.*, 2024). It predominantly affects women of reproductive age and manifests as asymptomatic brownish macules with irregular borders (Sreenath *et al.*, 2022; Honigman; Rodrigues, 2023). Its prevalence varies according to ethnic, environmental, and behavioral factors, and may reach more than 30-40% in populations with higher phototypes and intense sun exposure (Sabry *et al.*, 2025; Narde *et al.*, 2025).

Its pathogenesis is complex and multifactorial, involving ultraviolet radiation (UV), genetic predisposition and hormonal alterations, in addition to oxidative stress, inflammation, and interaction between keratinocytes, melanocytes and dermal components. Although it does not represent a life-threatening condition, the psychosocial impact is significant (Ribeiro *et al.*, 2025; Liao *et al.*, 2026).

Tyrosinase inhibitors are among the main therapeutic targets. However, available therapies present limitations related to efficacy, stability and adverse effects, such as cutaneous irritation and low permeation (Zolghadri *et al.*, 2023; González-Molina; Martí-Pineda; González, 2023). In this context, plant-derived compounds, especially flavonoids, have been investigated for their antioxidant, anti-inflammatory and melanogenesis modulating properties, with low cytotoxicity, highlighting quercetin and pomegranate oil, which present therapeutic potential in melasma management (El-Nashar *et al.*, 2021; Ha *et al.*, 2022; Marchiori *et al.*, 2023).

However, low bioavailability and limited skin permeation compromise the efficacy of these bioactives. Nanotechnology emerges as a promising strategy to optimize their delivery, promoting greater stability, permeation and controlled release, in addition to favoring biocompatibility and homogeneous distribution in skin layers (Ghasemiyeh; Mohammadi-Samani, 2020; Budama-Kilinc *et al.*, 2022; Mohd-Setapar *et al.*, 2022).

Given this context, the present article aimed to analyze advances in the understanding of melasma pathophysiology and discuss new therapeutic perspectives based on natural bioactives and nanotechnology, seeking to review the main molecular mechanisms involved in melasma pathogenesis, discuss the limitations of conventional therapies, evaluate the therapeutic potential of natural bioactive compounds, with emphasis on flavonoids, and analyze the role of nanostructured systems in optimizing skin delivery and enhancing the efficacy of these compounds.

2 METHODOLOGY

This study consists of a narrative literature review. The bibliographic search was conducted in the PubMed and Scopus databases, without time restriction, including studies published up to February 2026. The following descriptors were used in combination with Boolean operators: melasma, pathophysiology, oxidative stress, bioactive compounds, natural actives, plant extracts, and nanotechnology.

As inclusion criteria, original articles, reviews, and experimental studies published in English and Portuguese were considered, addressing melasma, its pathophysiological mechanisms, and/or therapeutic strategies, with emphasis on the use of antioxidant compounds and/or nanotechnology applied to the skin. Exclusion criteria included duplicate studies, book chapters, patents, editorials, conference abstracts, and studies not directly related to the proposed topic, as assessed by the authors.

After applying the eligibility criteria, a total of 119 articles was selected for the final analysis of this review.

3 RESULTS AND DISCUSSION

3.1 ADVANCES IN MELASMA PATHOPHYSIOLOGY: A MULTIFACTORIAL CONDITION

Melasma is an acquired and chronic hyperpigmentation disorder characterized by brown macules with irregular borders and symmetrical distribution in photoexposed facial areas. The condition presents three main clinical patterns, centrofacial, malar, and mandibular, with the centrofacial type being the most prevalent (Honigman; Rodrigues, 2022; Platsidaki *et al.*, 2024). It is considered the most common cause of facial pigmentation, predominantly affecting women of reproductive age and individuals with Fitzpatrick phototypes III-VI (Fitzpatrick, 1988; Hizli; Kiliç; Aytaç, 2024; Liao *et al.*, 2026).

Although traditionally described as an epidermal hyperpigmentation disorder, current evidence indicates that melasma represents a multifactorial skin condition involving genetic, hormonal, inflammatory, vascular and oxidative components in addition to melanocytic hyperactivity (Sarkar; Bansal; Gold, 2025; Ribeiro *et al.*, 2025). Family history has been identified as an important risk factor, with studies reporting positive familial occurrence in a significant proportion of patients and suggesting genetic susceptibility, including patterns compatible with autosomal dominant inheritance (Holmo *et al.*, 2018; Sarkar *et al.*, 2020; Liu; Chen; Xia, 2023; Platsidaki *et al.*, 2024).

Hormonal influences also play a central role in melasma pathogenesis. Estrogen and progesterone receptors expressed in the skin may stimulate melanogenesis and factors related to reproductive life, such as pregnancy, hormonal contraceptive use and hormone replacement therapy, have been associated with disease onset and worsening (Filoni *et al.*, 2018; Liu *et al.*, 2023; Platsidaki *et al.*, 2024; Breguedo *et al.*, 2024; Mpofana *et al.*, 2025). Estrogen signaling can increase MC1R expression and activate melanogenic pathways, although hormonal stimulation alone appears insufficient to induce hyperpigmentation without synergistic UV exposure (Handel; Miot; Miot, 2014; Cario, 2019; Natale *et al.*, 2016; Zhang *et al.*, 2025).

Recent advances have expanded the understanding of melasma beyond pigmentary alterations, highlighting the contribution of oxidative stress, chronic inflammation and dermal remodeling. Current evidence supports the concept that melasma results from complex cellular interactions involving epidermal and dermal components, which contribute to disease persistence and recurrence (Navya; Pai, 2022; Zheng; Pei; Yao, 2024; Ali; Niaimi, 2025).

3.1.1 Melanogenesis and Melanocytic Dysfunction

Melanin is produced by melanocytes, specialized cells responsible for cutaneous pigmentation and photoprotection. Melanin synthesis occurs within melanosomes and is transferred to keratinocytes, forming the epidermal melanin unit, where pigment deposition protects nuclear DNA against UV radiation (Fu *et al.*, 2020; Bento-Lopes *et al.*, 2023; Wang *et al.*, 2024). Melanogenesis is regulated by molecular signaling pathways involving the melanocortin-1 receptor (MC1R), activated by α-MSH and ACTH, which stimulate cyclic AMP signaling and increase tyrosinase activity and related proteins essential for melanin synthesis (Swope; Abdel-Malek, 2018; Hirobe, 2024; Abdalla, 2021; Slominski *et al.*, 2022).

In melasma, hyperpigmentation results mainly from melanocyte hyperactivity and hypertrophy rather than increased melanocyte number, leading to excessive melanin production in affected epidermal areas (Artzi *et al.*, 2021; Khunger *et al.*, 2020). Histopathological findings also demonstrate dermal involvement, including solar elastosis, increased vascularization, pendulous melanocytes and mast cell infiltration, reinforcing the multifactorial nature of the disorder (Esposito *et al.*, 2022; Honigman; Rodrigues, 2022; Zheng; Pei; Yao, 2024).

UV radiation and visible light represent major triggering factors. UV exposure induces reactive oxygen species (ROS), inflammatory mediators, and vascular factors, promoting melanogenesis through oxidative stress, DNA damage, and pro-inflammatory signaling. These mechanisms reinforce that melasma results from the interaction between melanocytic dysfunction, oxidative stress, inflammation, and structural dermal alterations (Alcantara *et al.*, 2020; Morgado-Carrasco *et al.*, 2021; Ansary *et al.*, 2021; Rattanawiwatpong *et al.*, 2025).

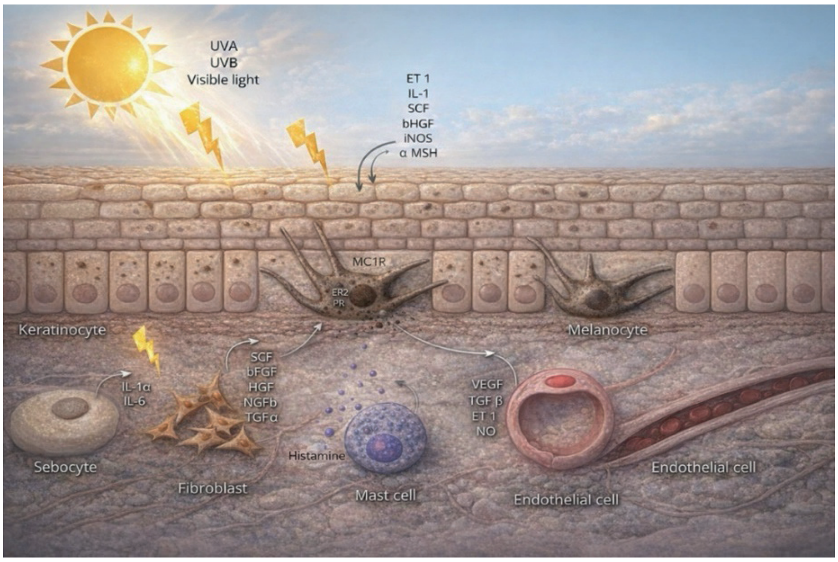
3.1.2 Effects of Ultraviolet Radiation Exposure in Melasma

UV radiation is the main modulator of skin pigmentation and the central stimulus for tanning (Passeron; Picardo, 2018). Evidence indicates that solar exposure is one of the main environmental factors involved in the development and worsening of melasma, since the condition occurs predominantly in photoexposed areas (Alcantara *et al.*, 2020; Sreenath *et al.,* 2022).

UV exposure induces the formation of ROS and the imbalance between their production and endogenous antioxidant systems results in oxidative stress, compromising cellular integrity (He *et al.*, 2023; Liao *et al.*, 2026). In melasma, beyond structural damage, ROS act as molecular signaling agents that stimulate melanocyte proliferation and intensify melanogenesis, contributing to the persistence and recurrence of hyperpigmentation (Hussen *et al.*, 2025). UV-induced damage stimulates keratinocytes to release several pro-melanogenic mediators, including stem cell factor (SCF), basic fibroblast growth factor (bFGF), interleukin-1 (IL-1), endothelin-1 (ET-1), and inducible nitric oxide synthase (iNOS) (Figure 1) (Fu *et al.*, 2020; Pietowska *et al.*, 2022).

In addition to the release of pro-melanogenic mediators, DNA damage induced by UV radiation stimulates the expression of the tumor suppressor protein p53 in keratinocytes, an important molecule involved both in genomic repair and in the regulation of pigmentary response. Activation of p53 increases the expression of proopiomelanocortin (POMC), which is cleaved into hormones such as ACTH and α-MSH. α-MSH binds to the melanocortin-1 receptor (MC1R) present in melanocytes, triggering activation of the cAMP pathway and promoting increased expression of melanogenic enzymes, including tyrosinase and tyrosinase-related protein-1 (TRP-1), both essential for melanin synthesis (Kumari *et al.*, 2018; Esposito *et al.,* 2022; Ali; Niaimi, 2025).

Figure 1 - Impact of UV radiation on skin affected by melasma.



Legend: UV radiation triggers melanogenic, oxidative, and inflammatory responses in the epidermis and upper dermis. Melanocortin (α-MSH) and its receptor (MC1R) are increased in keratinocytes and melanocytes. Nuclear estrogen-β (ER2) and progesterone receptors (PR) are stimulated. Growth factors are actively released by fibroblasts, including nerve growth factor-β (NGFβ), SCF, HGF, TGFα and bFGF. Endothelin-1 (ET-1) is secreted by keratinocytes and endothelial cells following UV exposure. Mast cells release histamine under paracrine stimulation and UVR exposure. Nitric oxide (NO), produced by inducible nitric oxide synthase (iNOS), is increased in the epidermis in melasma. Sebocytes mediate inflammatory responses by releasing pro-inflammatory cytokines IL-1 and IL-6.
Source: Image created with the assistance of artificial intelligence (ChatGPT, OpenAI, 2026).

Although melasma is considered predominantly an epidermal disorder, recent evidence indicates that dermal alterations, such as solar elastosis, cellular senescence, and extracellular matrix remodeling, play a fundamental role in hyperpigmentation. These findings reinforce the association between melasma, photoaging, and intrinsic aging, broadening the understanding of the disease as a structurally complex cutaneous process (Liu; Chen; Xia, 2022; Ali; Niaimi, 2025; Zhang *et al.*, 2025).

A study conducted by Kim *et al.* (2019) observed that senescent fibroblasts were mainly present in the upper layer of the lesional dermis, close to melanocytes, favoring interactions between these cells. This makes fibroblasts a contributing factor to melasma, since they are capable of secreting melanogenic factors that regulate pigmentation. Another study involving 50 women with a mean age of 36 years evaluated several histopathological characteristics of melasma skin compared with adjacent skin. Epidermal atrophy was observed in 90% of hyperpigmented skin samples, increased solar elastosis was noted in lesional skin compared with unaffected skin, and one of the most significant findings was the presence of pendulous melanocytes in approximately 76% of lesional skin (Gautam *et al.,* 2019). These findings strongly suggest that disruption of the basement membrane may prevent melanocytes from remaining in their original basal layer location, becoming an important factor in melasma worsening and recurrence (Wan *et al.,* 2023).

The combination of these mechanisms sustains oxidative stress and chronic inflammation in melasma pathophysiology, providing a biological basis for therapeutic approaches with antioxidant, anti-inflammatory, and melanogenesis-modulating actions.

3.2 CONVENTIONAL THERAPEUTIC APPROACHES AND THEIR LIMITATIONS

Topical treatments remain the cornerstone of melasma management. The main therapeutic objective is the inhibition of melanogenesis, especially through modulation of tyrosinase activity, reduction of melanocyte hyperactivity, and removal of pigment already deposited in the epidermis. Among the available strategies, topical therapies continue to be considered the first-line approach, based on the use of antimelanogenic agents (Neagu *et al.*, 2021; Mahajan *et al.*, 2022).

Hydroquinone is considered the gold standard in melasma treatment, acting through tyrosinase inhibition and blockage of the conversion of DOPA into melanin (Zheng; Pei; Yao, 2025). Despite its clinical efficacy, prolonged use is associated with adverse events such as irritant dermatitis, hypersensitivity, and exogenous ochronosis, which limits its continuous application (Liao *et al.,* 2026). Retinoids such as tretinoin, retinol, adapalene, and isotretinoin are also widely used, promoting cellular turnover, facilitating the penetration of other active compounds, and contributing to the dispersion of epidermal pigment. However, side effects such as peeling, burning sensation, and cutaneous irritation are frequently reported, which may

compromise treatment adherence and even cause damage to the skin barrier (Nasrollahi *et al.*, 2019; Sulliman *et al.*, 2025).

Combination therapy, initially proposed by Kligman and Willis in 1975, associating hydroquinone, tretinoin, and a corticosteroid, demonstrated greater clinical efficacy when compared to monotherapy. However, the high rate of cutaneous irritation led to reformulations of the classical combination (Kligman; Willis, 1975; Sahu *et al*., 2020).

Other depigmenting agents, such as glycolic acid, azelaic acid, kojic acid, cysteamine, tranexamic acid, and alpha-arbutin, have been used either alone or in combined therapies, showing variable clinical outcomes (Mahajan *et al*., 2015; Saeedi; Eslamifar; Kherzi, 2019; Atallah; Charcosset; Greige, 2020). However, despite the diversity of available tyrosinase inhibitors, concerns remain regarding sustained efficacy, lesion recurrence, and the occurrence of adverse effects, including cellular toxicity, irritation, and skin sensitization (Hassan *et al*., 2023).

Considering the multifactorial nature of melasma, which involves oxidative stress, inflammation, and dermal remodeling, an exclusively antimelanogenic approach appears limited. Therefore, therapeutic strategies are needed that act not only through tyrosinase inhibition but also through modulation of oxidative stress and inflammatory mediators involved in disease pathogenesis. In this context, natural bioactive compounds with antioxidant and anti-inflammatory properties have been widely investigated as safer and multifunctional alternatives (Thibane *et al*., 2019; Yu *et al*., 2022; Widelski *et al*., 2023). The use of these active compounds may contribute to the restoration of cutaneous redox balance and modulation of the inflammatory response, representing a promising therapeutic approach (Sarkar; Sahu, 2025).

3.3 NATURAL BIOACTIVES AS A THERAPEUTIC STRATEGY

The skin constitutes a highly specialized barrier against external agents, performing essential physical, chemical, and biological functions to maintain cutaneous homeostasis. However, skin affected by melasma presents a significant increase in oxidative stress biomarkers, including lipid peroxidation products and pro-inflammatory cytokines, characterizing a pro-oxidative and pro-inflammatory microenvironment. This imbalance suggests that chronic exposure to UV radiation and aggressive environmental factors may overwhelm endogenous antioxidant mechanisms, intensifying cellular damage and contributing both to melasma pathophysiology and skin aging (Lucio *et al*., 2023; Sarkar; Sahu, 2025).

In this context, plant-derived bioactive compounds emerge as promising therapeutic alternatives, acting on multiple mechanisms involved in melasma, including antioxidant, anti-inflammatory, photoprotective, and melanogenesis-modulating properties (Ko *et al*., 2021; Tomas *et al*., 2025). Among the main groups studied are flavonoids, phenolic acids, stilbenes, proanthocyanidins, and terpenoids, frequently extracted from fruits, leaves, roots, and bark of medicinal plants (Xian *et al*., 2021; Tanveer; Rashid; Tasduq, 2023; Zhao *et al*., 2025).

The relevance of this approach is closely related to the strong association between melasma and photoaging. Strategies aimed at reducing oxidative stress and UV-induced damage have demonstrated therapeutic potential, since ROS contribute both to melanocytic dysfunction and structural alterations in the skin. Thus, topical or systemic antioxidants may assist in ROS neutralization and cellular protection, reinforcing the role of plant-derived antioxidants in melanogenesis modulation and attenuation of photoaging effects (Speeckaert *et al.*, 2023; Miao *et al.*, 2025).

Recent studies have explored combined strategies involving plant-based actives to enhance antioxidant and depigmenting effects (Parvizi *et al.*, 2024; Elbouzidi *et al.*, 2025). Rattanawiwatpong *et al.* (2020) demonstrated that the topical association of vitamin E, vitamin

C, and raspberry leaf extract promoted significant improvements in skin color, elasticity, and luminosity after two months of use, suggesting possible functional synergism.

Several phytochemicals also exert direct effects on melanogenesis. Compounds such as gallic acid, quercetin, green tea extract and propolis act as tyrosinase inhibitors and modulators of melanogenic signaling pathways, reducing melanin production through competitive and regulatory mechanisms (El-Hawary *et al.*, 2022; Shin *et al.*, 2022; Widelski *et al.*, 2022; Okselni *et al.*, 2024). In addition to their depigmenting action, many of these compounds exhibit antimicrobial, regenerative, and extracellular matrix-stimulating effects, expanding their dermatological potential (Nisa *et al.*, 2024).

However, the clinical efficacy of these compounds depends on factors such as phytochemical composition, extract standardization, concentration, and skin permeation capacity. Extracts from pomegranate, green tea, quercetin, turmeric, and grape have demonstrated positive effects on inflammatory modulation, barrier function, and tissue recovery (Beken *et al.*, 2020; Dias; Pinto; Silva, 2021; Ren *et al.*, 2024). Resveratrol has been shown to prevent UV-induced collagen degradation, while apigenin demonstrated the ability to suppress UV-induced hyperpigmentation with a superior safety profile compared to conventional synthetic agents (Lin *et al.*, 2021; Farhan, 2024).

Therefore, plant-derived compounds represent multifunctional sources of therapeutic agents capable of acting simultaneously on oxidative stress, inflammation, and melanocytic dysfunction. The use of these bioactives, associated with strategies that optimize stability and bioavailability, may contribute to the development of safer and more effective topical therapies for chronic and recurrent skin conditions (Li *et al.*, 2023; Cordiano *et al.*, 2024; Salazar *et al.,* 2025).

Among the most promising compounds in this context are those with recognized antioxidant and anti-inflammatory activity, such as quercetin and pomegranate oil, whose biological properties and potential therapeutic synergy have attracted increasing scientific interest.

3.3.1 Quercetin and Pomegranate Oil: Biological Properties and Therapeutic Synerg

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) is a flavonoid widely distributed in fruits and vegetables and recognized as one of the most abundant phenolic compounds in the human diet (Ha *et al.*, 2022). Due to its hydroxyl-rich structure, quercetin exhibits strong antioxidant activity, particularly relevant in melasma, a condition strongly associated with oxidative stress (Zaborowski *et al.*, 2019; Batiha *et al.*, 2020).

Several studies have demonstrated its broad spectrum of biological activities, including antioxidant, anti-inflammatory, antibacterial, photoprotective, anti-aging, and depigmenting effects (Beken *et al.*, 2020; Lin *et al.*, 2021; Al-Khayri *et al.*, 2022; Okselni *et al.*, 2025). In addition to direct reactive ROS scavenging, quercetin modulates endogenous antioxidant defenses by increasing the expression of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Aghababaei; Hadidi, 2023; Amin *et al.*, 2025, Hana; Harwansh; Deshmukh, 2025).

Under UV exposure, quercetin has shown protective effects against skin damage by inhibiting inflammatory mediators and reducing collagen degradation. Experimental studies report inhibition of MMP-1 and COX-2 expression and modulation of signaling pathways related to photoaging and inflammation, including PKCδ and JAK2 (Tang *et al.*, 2019; Kant *et al.*, 2021; Zhou *et al.*, 2023; Shin *et al.*, 2019). Regarding pigmentation control, quercetin acts directly on melanogenesis by inhibiting tyrosinase activity and modulating melanogenic proteins such as TRP-1 and TRP-2, resulting in reduced melanin production (Choi; Shin, 2016; Fan *et al.*, 2017; Yang *et al.*, 2011).

Despite its therapeutic potential, topical application is limited by low moisture solubility, instability, and minimal permeation (David *et al.*, 2016; Carrillo-Martinez *et al.*, 2020). In this context, studies suggest that nanoencapsulation has emerged as an effective strategy to improve stability, solubility, and controlled release (Yazidi *et al.*, 2025; Tsichlis *et al* 2025; Ghasemiyeh; Mohammadi-Samani, 2020). Nanostructured systems, including lipid carriers, niosomes, and hydrogels, have demonstrated improved permeation, retention, and antioxidant and antityrosinase activity compared to conventional formulations (Lu *et al.*, 2019; Imran *et al.*, 2020; Lúcio *et al.*, 2023).

In general, the combination of quercetin with nanostructured delivery systems represents a promising strategy for the treatment of melasma, increasing the stability of the compound and optimizing its distribution to the epidermal and dermal layers involved in hyperpigmentation.

Similarly, natural vegetable oils have gained increasing attention due to their high content of bioactive compounds, including polyphenols, phytosterols, fat-soluble vitamins, and unsaturated fatty acids (Górnás; Rudzińska, 2016). Among them, pomegranate (*Punica granatum*) stands out for its antioxidant and anti-inflammatory properties, mainly attributed to polyphenols capable of neutralizing reactive ROS and modulating inflammatory pathways, which are highly relevant in skin disorders associated with oxidative stress and hyperpigmentation (Cordiano *et al.*, 2024).

Pomegranate seed oil, obtained by cold pressing, presents a lipid composition rich in punicic acid, ellagic acid, phytosterols, tocopherols, flavonoids, and other phenolic compounds, conferring antioxidant, anti-inflammatory, and regenerative potential (Ko; Dadmohammadi; Abbaspourrad, 2021; Valero-Mendoza *et al*., 2023; Siol *et al*., 2024). Ellagic acid, in particular, exhibits depigmenting activity through tyrosinase modulation and copper chelation, reducing melanogenesis while protecting against UV-induced collagen and elastin degradation (Kanlayavattanakul *et al*., 2020; Turrini *et al*., 2020; Wang *et al*., 2021).

Experimental studies have demonstrated that pomegranate derivatives reduce ROS levels, increase collagen synthesis, decrease MMP-1 expression, and attenuate oxidative and apoptotic damage induced by UV radiation, reinforcing their photoprotective and anti-inflammatory potential (Mariné-Casadó *et al*., 2022; Stefanou *et al*., 2021; Hamouda; Felemban, 2023; Bagińska *et al*., 2024).

The combination of pomegranate oil with other plant-derived bioactives may further enhance antioxidant and depigmenting effects through complementary mechanisms involving oxidative stress reduction, inflammatory modulation, and melanogenesis control (Table 1) (Baldi *et al*., 2023; Choi *et al*., 2024; Peng *et al*., 2024). Increasing interest in natural ingredients has encouraged the cosmetic industry to incorporate plant-based bioactives into topical formulations, driven by the search for safer, multifunctional, and sustainable therapeutic approaches (Almoraie *et al*., 2025).

Table 1 - Comparison between quercetin and pomegranate oil highlighting their main benefits for the skin.

Property/Activity	Pomegranate Oil	Quercetin
Antioxidant	Rich in polyphenols, ellagic acid, and punicic acid. Neutralizes ROS and protects the cell membrane (Mariné-Casadó *et al*., 2022)	Potent flavonoid that eliminates ROS and reduces lipid peroxidation (Ha *et al*., 2022)
Anti-inflammatory	Inhibits COX-2, NF-κB, and pro-inflammatory cytokines (IL-6, TNF-α) (Houston *et al*., 2017)	Reduces expression of inflammatory mediators (IL-1β, IL-6, TNF-α) (Okselni *et al*., 2024)
Antimelanogenic	Inhibits tyrosinase and regulates melanocyte activity (Turrini *et al.,* 2020)	Inhibits tyrosinase (Park *et al.,* 2018)
Photoprotective	Scavenges UVB-induced free radicals, reduces DNA and lipid damage (Afaq *et al*., 2009)	Protects keratinocytes from UV radiation, reduces erythema and inflammation (Shin *et al*., 2019)
Stimulation of skin regeneration	Stimulates fibroblast proliferation and collagen production, favoring tissue renewal (Mo *et al.,* 2014)	Promotes integrity of the epidermal skin barrier (Beken *et al*., 2020)

Source: Author's own construction.

Despite these benefits, topical application of pomegranate oil remains limited by low stability and susceptibility to oxidation, which may compromise bioavailability (Eid *et al*., 2024). Similar to quercetin, nanoencapsulation has been proposed to enhance physicochemical stability, protect bioactive compounds, and improve skin permeation and retention (Lopes *et al*., 2025). Nanostructured systems containing pomegranate oil, such as nanocapsules and nanoemulsions, have demonstrated improved antioxidant parameters and photoprotective effects against UVB-induced damage (Cervi *et al*., 2021; Marchiori *et al*., 2017).

Although natural ingredients present significant therapeutic potential, their efficacy is still limited by skin barrier permeability. In this context, nanostructured lipid carriers emerge as promising systems capable of protecting sensitive compounds, improving stability, and optimizing controlled release and skin delivery, enhancing the biological performance of encapsulated vegetable oils and flavonoids (Fitriani *et al.*, 2024; De Barros *et al.*, 2022; Marchiori *et al.*, 2023).

3.4 INTEGRATION BETWEEN NATURAL BIOACTIVES AND NANOTECHNOLOGY: FUTURE PERSPECTIVES

Nanoparticle-based delivery systems have attracted increasing interest due to their physicochemical properties, such as high surface area, encapsulation capacity, and modulation of active compound release. These systems generally consist of particles ranging from 1 to 1000 nm and can be developed from different biocompatible materials, allowing the incorporation of compounds with distinct physicochemical characteristics (Khezri; Saeedi; Dizaj, 2018).

In recent decades, nanocarriers have gained prominence in the pharmaceutical industry by enabling targeted delivery, controlled release, and the potential reduction of adverse effects

(Khan; Saeed; Khan, 2019). Subsequently, they were widely incorporated into the cosmetic industry for the development of formulations intended for skin, hair, and nails (Budama-Kilinc *et al.*, 2022; Ferraris *et al.*, 2022; Gupta *et al.*, 2022).

However, topical application of active compounds faces the skin barrier as its main obstacle, especially the stratum corneum, which represents the primary physicochemical barrier to the penetration of exogenous substances due to its dense cellular organization and high lipid content (Baroli, 2009; Salvioni *et al.*, 2021). Permeation may occur through follicular or transepidermal pathways (intercellular and transcellular) and is influenced by factors such as molecular weight, lipophilicity, formulation type, and the physical state of the stratum corneum (Garcês *et al.*, 2018; Bilal; Iqbal, 2020; Souto *et al.*, 2020).

In this context, nanotechnology emerges as a strategy capable of overcoming these limitations by promoting greater interaction with stratum corneum lipids, increasing lipid matrix fluidity, and optimizing cutaneous deposition (Ferraris *et al.*, 2021; Mascarenhas-Melo *et al.*, 2022). Several nanostructures have been explored, including liposomes, nanoemulsions, polymeric nanoparticles, and solid lipid nanoparticles, expanding the performance, stability, and bioavailability of topical active compounds (Gupta *et al.*, 2022; Salvioni *et al.*, 2021). Pioneer cosmetic products such as Capture Totale® (Dior) and Plenitude Revitalift® (L›Oréal Paris) demonstrated the feasibility of this approach in the market (Dubey *et al.,* 2022).

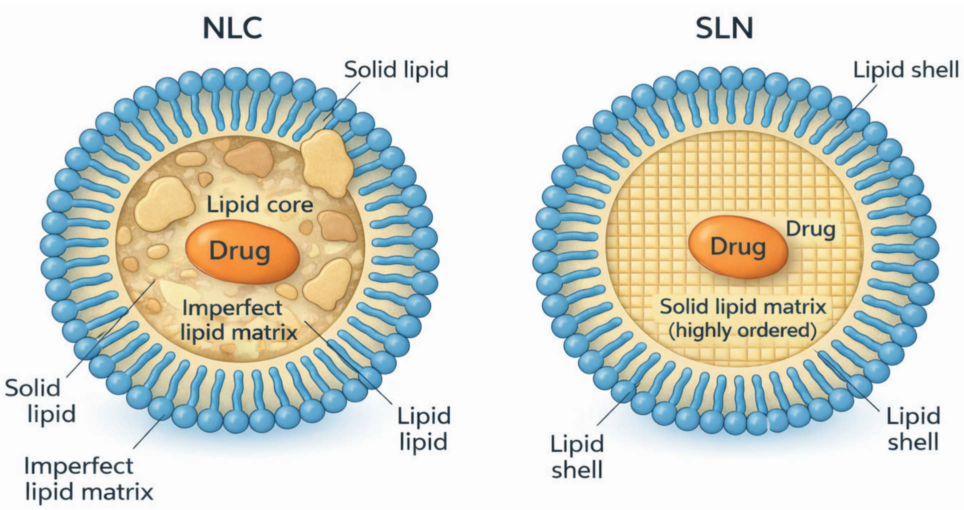
Lipid nanoparticles stand out due to their ability to increase skin permeation and retention, as well as to protect bioactive compounds against oxidative degradation, hydrolysis, and photochemical instability. Their high biocompatibility and safety profile make them particularly suitable for the delivery of flavonoids and vegetable oils, whose efficacy depends on the preservation of structural integrity and biological activity (Garcês *et al.*, 2018).

3.4.1 Second-Generation Lipid Nanocarriers: Principles and Technological Advantages

Lipid nanoparticles were introduced in the 1990s as an alternative to traditional colloidal systems, representing a new generation of formulations based on nanometric lipid matrices (Khezri; Saeedi; Dizaj, 2018). Among these platforms, nanostructured lipid carriers (NLCs) have been established as promising systems for topical administration, especially in dermatological applications (Souto *et al.*, 2020).

NLCs emerged as an evolution of solid lipid nanoparticles (SLNs), aiming to overcome limitations such as low incorporation capacity and possible active compound expulsion resulting from lipid recrystallization (Figure 2). Unlike SLNs, NLCs combine solid and liquid lipids in strategic proportions, forming a less organized and predominantly amorphous matrix. The presence of liquid lipid disrupts the crystalline arrangement, reducing the formation of highly ordered structures and minimizing the risk of active compound expulsion (Kharat; McClements, 2019; Teixeira *et al.*, 2020; Masiero *et al.*, 2021).

Figure 2 - Comparative schematic representation of a second-generation lipid nanocarrier (NLC) and a solid lipid nanoparticle (SLN), highlighting differences in lipid matrix organization and drug loading capacity.



Source: Image created with the assistance of artificial intelligence (ChatGPT, OpenAI, 2026).

This configuration provides NLCs with greater encapsulation capacity, improved physicochemical stability, and a more sustained release profile compared with SLNs. In addition, they present high biocompatibility, potential for skin hydration, and efficient dermal penetration (Borges *et al.*, 2020; Oliveira *et al.*, 2022).

The nanometric structure favors greater adhesion to the stratum corneum and may form an occlusive film that reduces transepidermal water loss. Encapsulation within a lipid matrix also protects sensitive compounds, such as antioxidants, retinoids, and UV filters, against oxidative and photochemical degradation, prolonging their stability and efficacy (Pardeike; Hommos; Muller, 2009; Ghate *et al.,* 2016; Ghasemiyeh; Mohammadi-Samani, 2020).

Experimental evidence reinforces these advantages. Alzahabi *et al.* (2019) demonstrated a significant increase in skin permeation of retinyl palmitate delivered through NLCs, highlighting the influence of physicochemical properties of the system on dermal delivery efficiency. Other studies indicate efficacy in the delivery of flavonoids and fatty acids, promoting antioxidant, anti-inflammatory, and depigmenting actions, with applications in photoaging, hyperpigmentation, and chronic inflammatory processes (Krambeck *et al.,* 2020; Hatem; El-Kayal, 2023; Fitriani *et al.,* 2024).

In the context of melasma, NLCs represent a particularly promising approach, as they integrate antioxidant protection, inflammatory modulation, and optimized cutaneous delivery within a single multifunctional system. This technology is especially relevant for natural bioactives, which are often unstable and present limited skin permeation, consolidating nanotechnology as a rational strategy in the development of more effective dermocosmetic formulations (Spanidi *et al.*, 2021; Mohd-Setapar *et al.*, 2022).

CONCLUSION

Melasma is a multifactorial disorder involving oxidative stress, inflammation, and dysregulation of melanogenesis, which requires integrated therapeutic strategies. In this context, plant-derived bioactives such as quercetin and pomegranate oil show significant potential due to their antioxidant, anti-inflammatory, and pigmentation-modulating properties, acting in a complementary manner.

The incorporation of these compounds into second-generation lipid nanocarriers emerges as a promising approach to overcome limitations related to stability and skin permeation, thereby enhancing their therapeutic efficacy.

Thus, the integration of natural actives and nanotechnology represents an innovative and pathophysiologically grounded strategy for the treatment of melasma. However, further clinical validation is still required to establish its applicability and standardize therapeutic protocols.

DECLARATIONS

Artificial Intelligence Usage Statement: During the preparation of this manuscript, the authors used ChatGPT (OpenAI, 2026) as a supportive tool for the conceptual creation and structuring of visual elements (figures) included in the study. The generated images were subsequently reviewed, refined, and validated by the authors based on scientific knowledge and relevant literature. The authors declare that they maintained full oversight of all generated content and assume complete responsibility for the accuracy, integrity, and scientific interpretation of the information presented in this article.

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