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REVIEW

The Exposome in Melasma: A Comprehensive Review of Etiology, Mechanisms, and Implications for Management

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Abstract: Melasma is a common pigmentary skin disorder characterised by symmetrical brownish patches on the face, which significantly impacts patients' quality of life. This article provides a comprehensive review of the latest research progress on melasma from the perspective of the exposome, a dynamic interactive model. The exposome encompasses all environmental exposures and their biological responses experienced by an individual throughout their lifespan. We systematically explore the synergistic pathogenic mechanisms of endogenous exposures (such as hormonal levels, oxidative stress, thyroid dysfunction, vitamin D metabolism and psychological stress) alongside specific exogenous exposures (such as ultraviolet, visible light radiation, air pollution, pharmacological agents, dietary habits and skincare practices) and general exogenous exposures (such as climate change) in the pathogenesis of melasma. This article reveals how multiple exposure factors converge on key pathways such as the MITF/AhR signaling axis, oxidative stress cycles, and the POMC neuroendocrine pathway, collectively driving the sustained activation of melanocytes and pigmentation. Traditional therapies primarily target already formed pigmentation, with limitations including high recurrence rates and addressing symptoms rather than root causes. Based on the exposome concept, future clinical management strategies need to shift towards proactive, comprehensive health management throughout the entire process. This includes thorough assessment of individual exposure risks, enhanced full-spectrum photoprotection, skin barrier repair, lifestyle adjustments (such as stress management, regular routines and antioxidant-rich diets), as well as combined reparative treatments. This review aims to integrate existing evidence to provide new perspectives on the aetiology of melasma and offer insights for developing personalised prevention and treatment strategies.

Keywords: melasma, exposome, ultraviolet radiation, oxidative stress, estrogen, air pollution

Introduction

Melasma, an acquired hyperpigmentation condition, is typified by symmetrically distributed, asymptomatic pigmented spots and patches on the face.[1] Based on its distribution patterns, it can be classified into three types: central facial (the most common), malar, and mandibular. Women, especially those of childbearing age (ages 20–50), are more likely to experience melasma.[2] These patches may negatively affect the psychological, social, and other facets of the life of those who are impacted because they are associated with cosmetic concerns.[3]

Melasma's pathophysiology is complicated and still insufficiently understood, involving complex interactions between genetic predisposition and a multitude of environmental factors. The key to comprehending the genesis of melasma is the interplay between lifelong environmental influences and genetic predisposition. To systematically analyze this complex web of interactions, the concept of the "exposome" provides a dynamic interactive model. Initially proposed by Wild, the exposome refers to the total exposure to environmental factors from birth to death.[4] Miller further refined it as "the cumulative measure of environmental influences and associated biological responses throughout the

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lifespan, including exposures from the environment, diet, behavior, and endogenous processes".[5] This paradigm shifts the research focus from isolated risk factors to the dynamic, cumulative, and interactive effects of multiple exposures.

The skin, as the primary interface with the external world, is uniquely positioned at the crossroads of the exposome. It is constantly subjected to exogenous assaults while being modulated by endogenous physiological states. Melasma exemplifies a condition where exogenous triggers and endogenous susceptibilities converge. A comprehensive understanding of its pathogenesis, therefore, necessitates moving beyond a linear cause-effect model towards an exposome-based approach that captures the synergy of these multifaceted influences. This review aims to synthesize recent progress in melasma research through the lens of the exposome. By adopting a structured framework that categorizes exposures into endogenous, specific exogenous, and general exogenous domains, and by examining their interactions through shared biological pathways, we seek to provide a more holistic understanding of melasma's etiology and offer insights for developing personalized prevention and management strategies.

The Exposome: A Dynamic Interactive Model for Dermatological Research and Its Application to Melasma

The exposome concept provides a robust paradigm for investigating complex, multifactorial diseases like melasma, where pathogenesis cannot be attributed to a single agent but emerges from the lifelong interplay between an individual's biology and their environment. The exposome is commonly categorized into three interrelated domains: (1) the endogenous exposome, encompassing factors originating from within the body such as hormonal fluctuations, metabolic processes, oxidative stress, psychological stress, and the microbiome; (2) the specific exogenous exposome, which includes directed exposures like solar ultraviolet (UV) and visible light radiation, air pollutants, dietary components, skincare products, and pharmacological agents; and (3) the general exogenous exposome, referring to broader contextual and societal factors like climate, socioeconomic status, and urbanization, which shape the intensity and nature of specific exposures.[6]

This tripartite classification has proven valuable in elucidating the etiology of other multifactorial dermatoses. For instance, in atopic dermatitis, research has demonstrated how endogenous factors (eg, immune dysregulation) interact with specific exogenous exposures (eg, irritants, aeroallergens) within a permissive general external environment (eg, low humidity, urban living) to drive disease onset and flares.[7] These research precedents demonstrate that adopting a global perspective through exposome, rather than focusing solely on individual factors, can more profoundly reveal the complex aetiology of skin conditions such as melasma.

The pathogenesis and progression of melasma is a classic example of the synergistic interaction of exposures in all three domains (Figure 1). Exogenous exposome and endogenous exposome do not operate in isolation. Instead, they exert additive or synergistic effects through convergent molecular pathways. For example, both UV radiation and hormonal changes can activate key signaling axes like the microphthalmia-associated transcription factor (MITF)/aryl hydrocarbon receptor (AhR) pathway, induce oxidative stress, and sustain a chronic inflammatory microenvironment in the skin.[8,9] This ultimately drives melanocyte hyperactivity and the formation of persistent pigmented patches. The general external environment, such as climate change leading to increased UV intensity and heat stress, can amplify these interactions. Therefore, adopting this dynamic interactive model is particularly apt for melasma, as it allows for a systematic deconstruction of how exposures from these interrelated domains collectively contribute to disease susceptibility, initiation, and perpetuation. The following sections will detail the roles and mechanisms of exposures within this endogenous and exogenous framework, specifically in the context of melasma.

Endogenous Exposome in Melasma

Oxidative Stress

The role of oxidative stress in the pathophysiology of melasma is becoming more widely acknowledged. Melanocytes are specialized cells responsible for synthesizing melanin.[10] Compared to normal skin, melanocytes in the epidermis of melasma lesions are overly active, which result in an overabundance of melanin synthesis. Higher levels of melanocortin 1 receptor (MC1R) and α-melanocyte-stimulating hormone (α-MSH) enhance melanocyte activity in the epidermis of

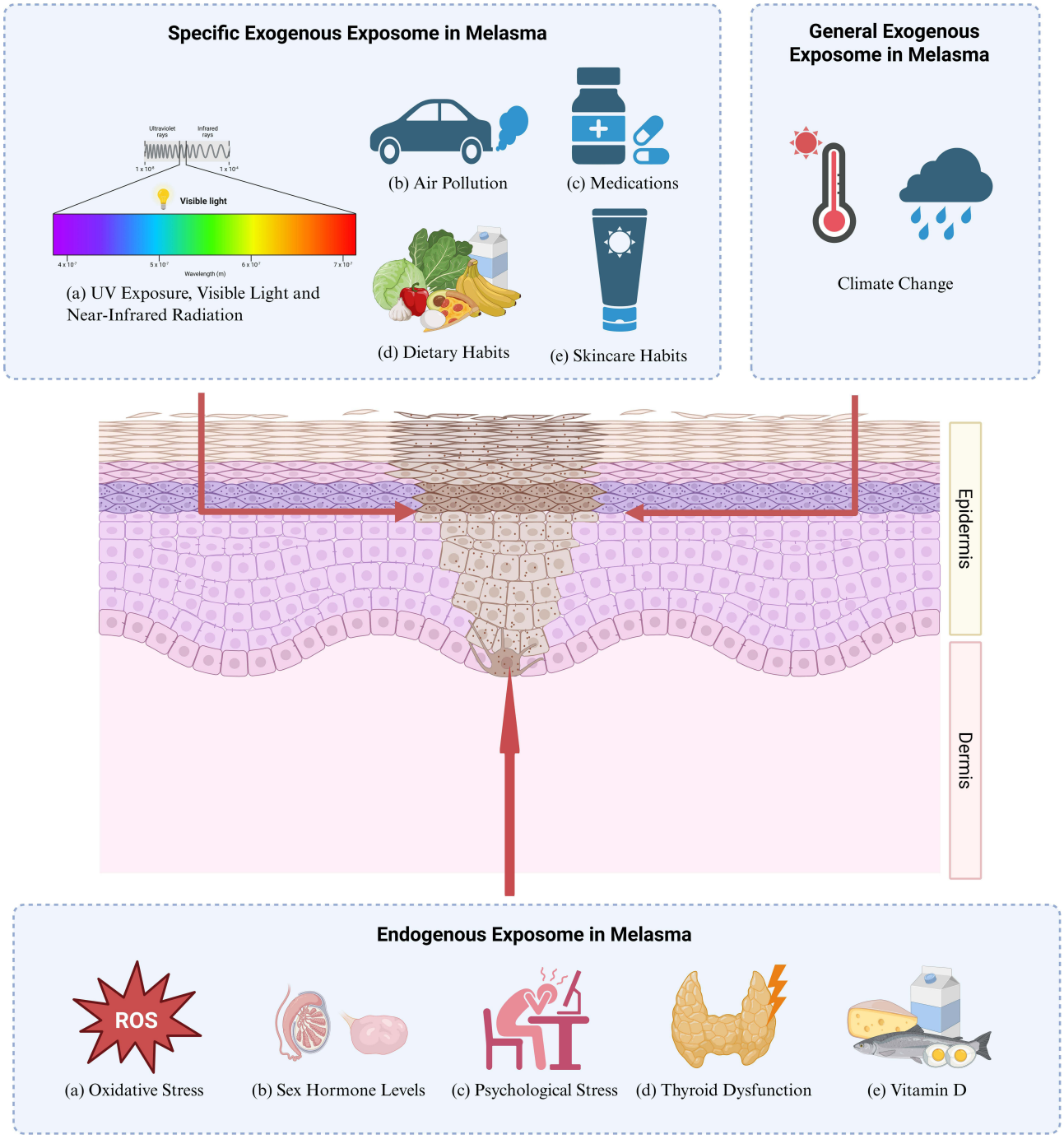

Figure 1 It has been established that these exposure factors are linked to melasma; either separately or in combination, they encourage and maintain the onset and progression of melasma.

melasma lesions. One essential transcription factor that controls the synthesis of melanin is microphthalmia-associated transcription factor (MITF). Various exposure factors such as hormones, UV light, inflammation, and oxidative stress directly activate MITF transcription through the cAMP/PKA pathway, Wnt/β-catenin pathway,[11,12] and SCF/c-KIT pathway,[8] or indirectly upregulate MITF through the NF-κB or MAPK pathways,[13] promoting melanin synthesis and transport. These environmental stressors can also cause a significant amount of reactive oxygen species (ROS) to be produced. Long-term accumulation of ROS can not only directly damage cells but also enhance MITF stability through the ROS-Nrf2/NF-κB axis, creating a vicious cycle with inflammation that exacerbates melanin deposition in melasma.

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Research has indicated a strong correlation between the degree of melasma pigmentation and elevated levels of oxidative stress in the skin.[14]

Research has shown that the aryl hydrocarbon receptor (AhR) is also involved in mediating ROS-dependent inflammatory responses in keratinocytes and promotes the formation of melanin in melasma. All of the main skin cells contain the cytoplasmic transcription factor AhR, which is triggered by a variety of environmental stresses.[15] Long-term activation of skin AhR signaling has been demonstrated to be a key factor in skin pigmentation induced by tobacco smoke and UVB radiation.[16] In addition to causing the initial inflammatory phase of melasma, oxidative stress may also maintain melanocyte activation through persistent inflammation. In order to create targeted treatments that might address pigmentation and possible inflammatory processes, it is essential to comprehend how oxidative stress contributes to melasma.

Sex Hormone Levels

Progesterone and estrogen have a direct correlation with the development and exacerbation of melasma. Melasma occurs at a significantly higher rate in women of childbearing age compared to men. Additionally, 40–50% of pregnant women and oral contraceptive users develop melasma. Estrogen receptors (ER) and progesterone receptors (PR) are upregulated in melasma lesions, especially around blood vessels and in fibroblasts, suggesting that sex hormones may be involved in the development of melasma.[17] Research has shown that the use of selective estrogen receptor modulators or drugs that inhibit estrogen synthesis can improve melasma.[18]

Estrogen stimulates keratinocytes and melanocytes to release melanogenic substances like α-MSH and SCF, upregulating tyrosinase activity and MITF expression, which increases melanin synthesis.[19] Notably, research indicates that even at pregnancy doses, estrogen alone cannot induce melanin formation; however, when combined with UV light and sebocyte-conditioned media, it can significantly activate the paracrine effects of fibroblasts and sebocytes, enhancing pigmentation.[20] Changes in estrogen and progesterone levels are one of the triggers for melasma, which may exacerbate oxidative stress and lead to abnormal activation of melanin production-related signaling pathways such as MAPK/ERK.[21] Furthermore, the pathophysiology of melasma is linked to the regulation of the gut-skin axis. One particular type of microbiota seen in melasma patients is *Collinsella spp*.[22] By altering estrogen metabolism, their biological effects might be a important factor in the formation of melasma.

It is worth noting that progesterone plays two roles in melasma: first, it may promote melanin synthesis through receptor activation; second, it may prevent melanocytes from proliferating, with the specific effects potentially depending on the local microenvironment (such as UV exposure, inflammatory factors, etc).[23] Future studies need to further clarify the mechanisms of progesterone's action at different pathological stages to guide targeted treatments.

Psychological Stress

Stress-related skin disorders such as malignant melanoma and atopic dermatitis are associated with dysregulation of the Proopiomelanocortin (POMC) system,[24] and similar pathways may exist in the pathogenesis of melasma, particularly with the overactivation of α-MSH. POMC is a precursor protein that is cleaved by tissue-specific enzymes to produce various bioactive peptides, including adrenocorticotropic hormone (ACTH), α-MSH, β-MSH, γ-MSH, and β-endorphin. In order to regulate physiological processes like the body's stress response, immune modulation, pigmentation, energy metabolism, and appetite, these peptides bind to melanocortin receptors (MCRs).[25] In the pathological process of melasma, the POMC derivative α-MSH can bind to the MC1R receptor on skin melanocytes, activating tyrosinase activity and promoting melanin synthesis, a process that may be enhanced under UV exposure or stress stimuli.[26]

Therefore, POMC regulates melanin synthesis through its derivatives and may be a key link connecting stress responses, UV exposure, and the pathological mechanisms of melasma. Patients with melasma commonly experience psychological stress and disruptions in biological rhythms. A recent cross-sectional study involving questionnaires and objective measurements of 108 melasma patients and 111 healthy controls found that indicators of biological rhythm disruption—such as stress or anxiety tendencies (61.1% in patients vs. 37.8% in controls, P=0.001), irregular eating patterns (29.6% vs. 11.7%, P=0.002), inconsistent sleep schedules (38.9% vs. 25.2%, P=0.016), frequent night shifts (22.2% vs. 15.3%, P=0.004), and staying up late (38.9% vs. 29.7%, P=0.047)—were significantly associated with the

occurrence of melasma. Additionally, stress or anxiety tendencies significantly affected the patients' melanin index ratio (MI ratio, P=0.014), indicating a correlation between stress and the severity of pigmentation.[27] These results support the idea that long-term stress may activate POMC expression through the HPA axis, thereby indirectly promoting melanin synthesis.[28] Nevertheless, a clear causal link between POMC and melasma has not yet been established by the literature. Additionally constrained by its design, the previously mentioned cross-sectional study is unable to determine causality. However, the interplay of stress, biological rhythm disturbances, and the POMC system offers possible avenues for further investigation into the neuroendocrine mechanisms underlying melasma.

Thyroid Dysfunction

The association between thyroid dysfunction and melasma has been receiving increasing attention. A meta-analysis including seven studies, comprising a total of 473 melasma patients and 379 controls, showed that serum thyroid-stimulating hormone, anti-thyroid peroxidase antibodies, and anti-thyroglobulin antibody levels were significantly higher in melasma patients compared to the non-melasma control group, with this difference being more pronounced in female patients.[29] Epidemiological research data support this association. A case-control study involving 70 non-pregnant women with melasma found that the overall prevalence of thyroid dysfunction in the patient group was 18.5% (mainly hypothyroidism), significantly higher than the 4.3% observed in the control group.[30] Another large observational study conducted among the Greek population also found that 21% of 150 patients with melasma had thyroid disease.[31]

However, the specific role of thyroid hormones in the pathogenesis of melasma remains unclear. The two may share certain pathophysiological pathways, such as chronic low-grade inflammation or oxidative stress, rather than a simple causal relationship. A preliminary study compared the severity of melasma in patients with hyperthyroidism before and after three months of antithyroid treatment, finding no significant improvement in the modified Melasma Area and Severity Index (mMASI) scores following treatment.[32] This suggests that simply correcting thyroid dysfunction may be insufficient to rapidly improve melasma, as the two conditions may be influenced by common genetic or environmental factors, or be linked through more complex interactions.

Most current evidence comes from cross-sectional studies, which cannot establish causality. Future research needs to adopt prospective designs to clarify whether thyroid autoimmunity or dysfunction is a trigger, a coexisting condition, or a consequence of melasma, and to provide higher-level evidence on whether thyroid disease screening is necessary for patients with melasma in clinical practice.

Vitamin D

The role of vitamin D and its receptor in skin pigment metabolism makes them potential endogenous risk factors for melasma. Vitamin D exerts its biological effects through its nuclear receptor (Vitamin D Receptor, VDR), which is expressed in various skin cells including keratinocytes, fibroblasts, and melanocytes.[33] 1,25-dihydroxyvitamin D can increase tyrosinase activity and stimulate melanin production.[34] Therefore, the functional status of VDR may influence susceptibility to melasma. At the same time, genetic research has provided evidence for this. A case-control study involving Egyptian women found that the TaqI polymorphism of the VDR gene was significantly associated with the risk of melasma. Individuals carrying the (tt) genotype and the (t) allele had their risk of developing melasma increased by 5.44 times and 3.37 times, respectively.[35] This study suggests that genetic variations in the VDR gene may contribute to the pathogenesis of melasma by affecting receptor function or vitamin D metabolism.

Epidemiological studies have also observed abnormal vitamin D levels in patients with melasma. A cross-sectional study showed a significant difference in serum vitamin D levels between melasma patients and healthy controls (p=0.050).[36] Another large observational study conducted among a Greek population similarly found that 22% of 150 patients with melasma had mild vitamin D deficiency.[31] Notably, in this study, the average MASI scores of patients with vitamin D deficiency were higher than the overall patient mean, suggesting that vitamin D levels may be associated with disease severity.

However, current research on the exact mechanism of vitamin D in melasma remains insufficient, and most studies are cross-sectional, making it impossible to establish causality. The lower vitamin D levels in patients with melasma may be related to their active avoidance of sun exposure due to aesthetic concerns, while sun exposure is a key pathway for

the skin to synthesise vitamin D.[31] Therefore, whether vitamin D deficiency is a cause or a consequence of melasma remains to be further clarified through prospective studies. Future research is necessary to verify the role of VDR gene polymorphisms in different populations and ethnic groups, and to explore whether vitamin D supplementation has therapeutic or adjunctive value for melasma.

Specific Exogenous Exposome in Melasma

UV Exposure

UV radiation is an important environmental component that contributes to the development of melasma. UVA, UVB, and UVC are the three wavelength-based categories of electromagnetic radiation in the sun spectrum that have wavelengths between 100 and 400 nm.[37] UVA has strong penetration, reaching the dermis, where it cause ROS to be produced, damaging collagen and elastic fibers in the dermal matrix. It also stimulates melanocyte activity and promotes melanin synthesis and transport by directly or indirectly activating the MITF transcription factor. Prolonged UVA exposure leads to chronic skin inflammation and increased melanin synthesis, which is closely related to the recurrence and worsening of melasma.[38] UVB has a wavelength range of 290–320 nm and is characterized by higher energy, primarily affecting the epidermis. It activates the enzyme tyrosinase in epidermal melanocytes, promoting the conversion of tyrosine to melanin, resulting in short-term pigmentation. UVB can also cause sunburn and direct DNA damage, indirectly activating inflammatory responses and oxidative stress, exacerbating melasma pigmentation.

Ultraviolet (UV) light induces the formation of melasma through various mechanisms, including abnormal activation of melanocytes, changes in skin structure, increased oxidative stress,[39] and adaptive responses of melanocytes. Research has found that melanocytes in melasma-affected areas exhibit higher baseline activity after UV exposure, while melanocytes in the surrounding normal skin show greater adaptive capacity. After UV exposure, melanocytes in the healthy skin around melasma transfer a large amount of melanin to keratinocytes by increasing the transport of "melanosome-like melanin", leading to intensified pigmentation.[40,41] This phenomenon indicates that melasma development is directly associated with the surrounding skin's reactive capacity in addition to melanocyte activity. Therefore, effective sun protection measures are crucial for individuals at risk of melasma, especially in areas with high UV exposure.[42]

Visible Light and Near-Infrared Radiation

The wavelength range of visible light (VL) is 400–700 nm. Melasma lesions and the surrounding normal skin can both produce more melanin when exposed to visible light, particularly blue-violet light. Moreover, pigmentation induced by visible light is more persistent than that caused by UVA and UVB.[41] Research indicates that 415 nm blue light can activate OPN3, triggering calcium signaling pathways involving CAMKII, CREB, ERK, and p38, which upregulate MITF and tyrosinase, increasing tyrosinase activity and melanin formation, which can cause melasma to recur or worsen.[43–45] Blue light may also cause hypersensitivity reactions in the skin, resulting in redness, inflammation, and potentially exacerbating existing skin conditions such as melasma and other pigmentation disorders.[46] Near-infrared radiation (NIR) can activate fibroblasts, promote the expression of matrix metalloproteinase (MMP-1), degrade collagen, disrupt the skin barrier, and indirectly enhance melanin transfer.[45,47,48] As more artificial light sources are used in urban lighting, the potential impact of visible light and NIR on skin conditions like melasma warrants further investigation and could inform prevention strategies and treatment options for patients with melasma.

Air Pollution

Air pollution has become an important environmental factor affecting skin health, particularly in relation to pigmentation disorders such as melasma. Harmful substances in the air, such as fine particulate matter, heavy metals, and volatile organic compounds, can penetrate the skin barrier. Air pollution can directly damage skin cells through ROS and induce oxidative stress, affect melanocyte signaling pathways, and accelerate skin aging through various mechanisms, leading to local inflammation and oxidative stress responses that promote melanin production.[49] Research indicates that air pollution, such as tobacco smoke, can chronically activate skin AhR signaling, inducing skin pigmentation.[50,51] The

cumulative effects of these environmental irritants can lead to the development of melasma, especially in individuals with pigmentation disorders.

Additionally, the interaction between UV radiation and air pollution exposes the skin to both oxidative stress and inflammatory mediators, further exacerbating pigmentation issues. As urbanization continues to rise, understanding the relationship between air quality and skin conditions has become increasingly important for public health and dermatological practice. Strategies to reduce exposure to air pollutants, such as using protective skincare products and maintaining a clean environment, may help decrease the incidence of melasma.

Pharmacological Agents

Medications are an important component of exogenous exposure factors for melasma and can induce or exacerbate hyperpigmentation. A large-scale case-control study involving a diverse population in the United States confirmed that the use of pigmentation-inducing drugs is a significant risk factor for melasma, with odds ratios (OR) elevated across different racial groups (African Americans: OR=2.22; Hispanics: OR=2.03; Whites: OR=2.00; Asians/Pacific Islanders: OR=2.01).[52] This finding reveals a previously underappreciated role of drug exposure in the pathogenesis of melasma.

Changes in pigmentation are known side effects of some medications, including nonsteroidal anti-inflammatory drugs, chemotherapy agents, and antiepileptic drugs. Melasma may develop or worsen as a result of these medications' direct stimulation of melanin production or phototoxic reactions that raise the skin's sensitivity to UV light. Many chemotherapy medications, such as fluorouracil, capecitabine, and paclitaxel, are linked to photosensitive reactions. These reactions can cause localized or diffuse pigmentation after UV exposure, which can last for months or even years. Significant photosensitivity is also associated with targeted anticancer medications, such as the BRAF inhibitor vemurafenib and the RET inhibitor vandetanib. Patients treated with vemurafenib may experience photosensitive reactions at rates as high as 35% to 63%.[53] The pathological processes of melasma may overlap or work in concert with these drug-induced phototoxic reactions and the ensuing post-inflammatory pigmentation. In order to identify potential iatrogenic factors, a thorough medication history is essential in the clinical evaluation of melasma patients.

Dietary Habits

Research has shown that sebaceous cells have also been linked to the formation of melasma. When melanocytes are co-cultured with sebaceous cell lines, sebaceous cells can promote the formation of melanocyte dendrites and melanin production. Sebum cells can release a variety of cytokines and growth factors, including IL-1α, IL-6, angiogenin, and adipokines, and are likewise regulated by CY-MSH. This suggests that the paracrine actions of sebum cells may also play a role in the pathophysiology of melasma.[54,55] Therefore, reducing unhealthy dietary fat intake may help prevent and treat melasma.

Alcohol consumption, high-sugar and high-fat diets, and specific nutrients affect the onset and progression of melasma through oxidative stress, inflammation, and immune pathways. These dietary habits are modifiable risk factors for melasma. A high-fat, high-sugar diet (HFHSD) has been shown to exacerbate skin diseases by causing gut microbiota imbalance and immune dysregulation.[56] In eczema models, the combination of HFHSD and a humid, hot environment intensifies oxidative stress and inflammatory responses, leading to impaired skin barrier function and increased mast cell infiltration.[57] Given that alterations in gut microbiota can control systemic inflammation and hormone levels, such diets may also have an impact on fibroblast signaling and sebaceous gland cell activity, despite the paucity of direct evidence in melasma.[58]

Recent evidence from a case-control study of 150 Chinese patients highlights novel dietary factors. Alcohol intake emerged as a strong risk factor for melasma (adjusted OR: 20.05), possibly due to ethanol-induced hyperpigmentation via aldehyde dehydrogenase pathways or synergistic effects with UV exposure.[59]

The Mediterranean diet, characterized by a high consumption of fruits, vegetables, and olive oil, has been demonstrated to lower the risk of melanoma and improve skin health, likely due to its anti-inflammatory and antioxidant properties.[60] Diets high in antioxidants such as vitamins C and E, polyphenols, and omega-3 fatty acids can alleviate UV-induced skin damage by neutralizing ROS and preventing pro-inflammatory cytokines.[59] In photoaging models, for

instance, resveratrol and green tea catechins have been shown to improve skin elasticity and decrease pigmentation.[58] Melasma may be lessened by these eating practices.

Skincare Habits

Skincare habits have a significant impact on the course of melasma. Recent research employing lipidomics has revealed abnormalities in the skin surface lipids of female melasma patients. Compared to non-lesional skin, lesional skin shows a significant increase in total lipids, phosphatidic acid, phosphatidylserine, and ceramides (Cers), which may represent a compensatory mechanism to maintain skin barrier function compromised in melasma. Certain ceramide species, such as Cer[AH], exhibit a negative correlation with the activation level of melanocytes within the lesions, suggesting that a deficient skin barrier may be permissive for melanocyte hyperactivity.[61] This underscores the importance of using moisturizers containing barrier-repairing ingredients like ceramides.

By creating chemical and physical barriers that lessen UV ray penetration into the skin, sunscreens prevent the synthesis of melanin and pigmentation.[42] Thus, developing a sun protection habit is essential to improving melasma prognosis. However, some patients with facial pigmentation use insufficient amounts of sunscreen because they mistakenly think that darker skin naturally protects against UV rays. Research indicates that while melanin provides some photoprotection, additional sunscreen protection is still required, particularly for photosensitive conditions like melasma.[62]

The skin microbiome, an emerging component of the exposome, is also influenced by skincare routines. A pilot study suggests that the use of moisturizers may beneficially modulate the skin microbiome by promoting the abundance of commensal bacteria such as Staphylococcus epidermidisand *Staphylococcus hominis*, which are known to support skin health and may protect against pathogen colonization.[63] Furthermore, the use of sunscreen has been associated with helping to retain a healthier skin microbiome composition, potentially offering an additional layer of protection against dysbiosis linked to inflammatory skin conditions.[63] This highlights the interplay between sunscreen use, microbial ecology, and skin health.

Additionally, products containing ingredients such as vitamin C and niacinamide can help lighten the skin and reduce pigmentation. Antioxidants, by scavenging free radicals and alleviating oxidative stress, not only reduce the occurrence of pigmentation caused by environmental factors but also enhance the effectiveness of laser treatments.[49] It is crucial to note that harsh cleansing or over-exfoliation can disrupt the skin's lipid barrier,[64] potentially exacerbating melasma.

Unsafe whitening practices may complicate melasma and even trigger other pigmentary disorders. Some mercury-containing whitening products may harm the skin's protective layer, resulting in inflammation, rashes, and infections, which may worsen pigment metabolism disorders in melasma-affected areas.[65] Mercury can also interfere with melanin production and metabolism, potentially causing localized pigment loss or rebound hyperpigmentation.

General Exogenous Exposome in Melasma

Climate Change

Melasma and other pigmentary disorders are made worse by climate change in a number of ways, both directly and indirectly. Increased exposure to UV radiation, a known cause of melanogenesis and melasma incidence, has been brought on by rising global temperatures and stratospheric ozone depletion, especially in vulnerable populations.[37,38] Notably, regional studies highlight the synergistic role of heat and humidity in aggravating melasma severity. A large multicentric cross-sectional study from India involving 1001 patients demonstrated that prolonged exposure to cooking fire or occupational heat was significantly associated with higher melasma severity scores (modified MASI, P=0.003), with a positive correlation observed between heat exposure duration and disease intensity.[66] This suggests that localized thermal stress, amplified by climate change-induced temperature anomalies, may directly promote inflammatory and oxidative pathways in melanocytes.

Experimental models further elucidate the mechanisms linking damp-heat environments to skin pigmentation. In a BALB/c mouse model simulating climate change conditions, combined damp-heat exposure (35°C, 95% humidity) and high-fat/high-sugar diet synergistically worsened eczema-like lesions by inducing oxidative stress, immune imbalance (Th1/Th2 and Th17/Treg dysregulation), and gut microbiota alterations.[57] Although this model focused on eczema, the

pathways involving AhR activation, ROS accumulation, and chronic inflammation are analogous to melasma pathogenesis.[51] These findings imply that climate change-related humidity and temperature fluctuations can disrupt skin barrier function and amplify melanocyte hyperactivity through systemic inflammation.

Melasma risk may also be indirectly impacted by changes in living conditions brought on by climate change. Change of residence was found to be a protective factor (OR: 0.03) in a case-control study of 150 Chinese patients, possibly as a result of lower exposure to air pollutants.[59] By producing ROS and triggering melanogenic signaling pathways, climate change-related air pollution and extreme weather events can exacerbate UV effects.[49,50]

Integrative Pathways and Translational Perspectives

The evidence synthesized in this review underscores that the diverse array of endogenous and exogenous exposures implicated in melasma pathogenesis converge on a limited set of pivotal molecular pathways (Figure 2). Central to this convergence is the MITF/AhR signaling axis, which is activated by a wide spectrum of triggers, from ultraviolet radiation and airborne pollutants to hormonal fluctuations, thereby driving sustained melanocyte hyperactivity and melanogenesis.[8,15,51] This process is critically amplified by oxidative stress, which not only induces initial damage but

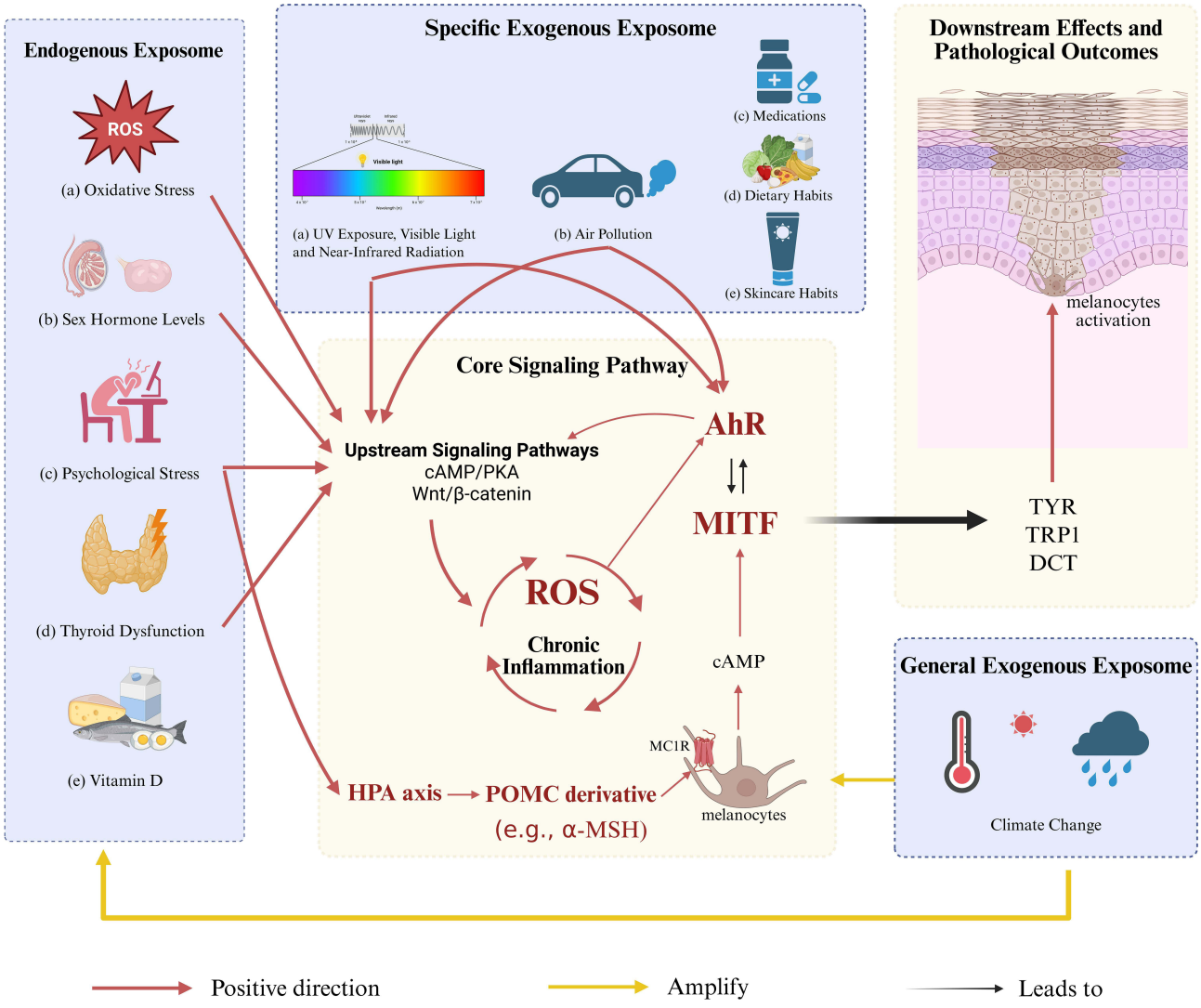

Figure 2 This schematic illustrates how endogenous, specific exogenous, and general exogenous exposures synergistically act on melanocytes, driving melasma through a set of core pathways. The central MITF/AhR signaling axis is activated by diverse triggers. Oxidative stress creates a self-amplifying loop that perpetuates inflammation. The POMC-derived neuroendocrine pathway links psychological stress and circadian disturbances to melanogenesis. These convergent signals lead to sustained melanin overproduction.

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Table 1 Treatment Strategies for Melasma: From Traditional Therapies to Exposome-Based Approaches

	Current Conventional Therapy	**Future Exposome-Based Management**
Core Concept	Interventions targeting established pigmentation.	Comprehensive prevention and regulation of lifelong internal and external exposure risks for individuals.
Primary Target	Focusing on the facial pigmentation spots themselves, the main approach targets the downstream process of melanin production.	Covers the skin, the internal environment of the whole body, and the external living environment.
Key Strategies	Topical agents: Hydroquinone, tranexamic acid, retinoids.	1. Conduct a comprehensive assessment of individual risk exposure: thoroughly inquire about life history, environmental contacts, stress, sleep, and other factors.
	Chemical peels and photoelectric treatments: such as acid peels, Q-switched/picosecond lasers, etc.	2. Enhanced and targeted protection: consistently use broad-spectrum sunscreen that also blocks blue light, and implement measures against air pollution.
	Systemic: Oral tranexamic acid.	3. Lifestyle adjustments: managing stress, maintaining a regular routine, avoiding high-fat and high-sugar diets, reducing alcohol intake, and adopting an antioxidant-rich diet.
	Broad-spectrum sunscreen.	4. Combined restorative treatment: Based on the management of the exposed group, use skincare products that repair the skin barrier, reduce inflammation, and provide antioxidant effects, while cautiously selecting photonic and electrical therapies as adjuncts.

also perpetuates a chronic inflammatory microenvironment and stabilizes MITF via the ROS-Nrf2/NF-κB pathway, creating a self-reinforcing cycle that exacerbates pigmentation.[13,14] Furthermore, the POMC-derived neuroendocrine pathway, particularly through α-MSH, establishes a direct link between psychosocial stress, circadian rhythm disturbances, and the activation of melanogenic signaling, highlighting a salient mind-skin connection.[25–27] The observed spatial heterogeneity in melanocyte adaptation between lesional and perilesional skin further illustrates the complex, tissue-specific outcomes of these exposure interactions.[40,41]

However, traditional treatment strategies for melasma have significant limitations. The current mainstream approaches mainly focus on inhibiting melanin synthesis or removing already formed pigmentation. Although these methods can improve appearance in the short term, they are often accompanied by a high recurrence rate and may cause adverse reactions such as post-inflammatory hyperpigmentation in some patients.[67–69] The fundamental reason is that these therapies primarily target the end manifestations of the condition, rather than intervening in the upstream exposure network that leads to the sustained activation of melanocytes (such as chronic oxidative stress, microinflammation, vascular abnormalities, and dermal structural changes). Treatment outcomes from this method frequently do not correspond with improvements in patients' long-term quality of life.[70]

Therefore, to overcome the current bottleneck in melasma treatment, a conceptual shift is necessary: moving from passive, localised patch treatment to proactive, whole-process health management based on individual exposure profiles. Table 1 clearly contrasts the fundamental differences between these two treatment models.[68,69,71,72]

Conclusion

Melasma is a typical pigmentary disorder of the skin caused by the synergistic effects of multiple factors. This article systematically elucidates, through a dynamic interactive model, how endogenous and exogenous exposome such as ultraviolet/visible light, air pollution, hormonal fluctuations, oxidative stress, and lifestyle collectively act on core signalling axes like MITF/AhR, driving the sustained activation of melanocytes and pigmentation.

Research from the perspective of the exposome has brought important insights to the clinical management of melasma. Firstly, clinical assessment should shift from traditional medical history inquiries to a comprehensive evaluation of exposure groups, proactively investigating modifiable risk factors including diet, skincare habits, occupational heat exposure, and biological rhythms. Secondly, treatment strategies need to adopt multi-target combined interventions, encompassing enhanced full-spectrum photoprotection, skin barrier repair, and the use of antioxidants, among other approaches, to simultaneously address multiple converging pathways. Future research in this field should focus on making breakthroughs in several key areas. Primarily, more prospective cohort studies are required to clarify the causal sequence between thyroid dysfunction, vitamin D metabolism disorders, and the onset of melasma, thereby providing high-level evidence for clinical screening and comorbidity management. Furthermore, for exposure factors such as the

skin and gut microbiomes, which have not yet been fully elucidated, their specific molecular mechanisms warrant in-depth investigation, which will aid in identifying new targets for disease intervention.

Abbreviation

UV, ultraviolet; MC1R, melanocortin 1 receptor; α-MSH, α-melanocyte-stimulating hormone; MITF, microphthalmia-associated transcription factor; ROS, reactive oxygen species; AhR, aryl hydrocarbon receptor; ER, Estrogen receptors; PR, progesterone receptors; POMC, Proopiomelanocortin; ACTH, adrenocorticotropic hormone; MCR, melanocortin receptor; VL, visible light; NIR, Near-infrared radiation; MMP-1, matrix metalloproteinase; OR, odds ratios; HFHSD, high-fat, high-sugar diet; Cer, ceramide; VDR, Vitamin D Receptor; Mmasi, modified Melasma Area and Severity Index.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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