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REVIEW ARTICLE

Impact of ultraviolet radiation and exposome on rosacea: Key role of photoprotection in optimizing treatment

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Abstract

Background: Pathophysiology of rosacea is not completely understood and involves a complex interaction among genetics, ultraviolet (UV) light, microorganisms, impaired skin barrier, neuronal and vascular dysfunction, and immune system disruption.

Aims: To describe the etiology of rosacea with an emphasis on the role of UV radiation and exposome, and to review the importance of non-pharmacologic strategies focusing on photoprotection.

Methods: We conducted a narrative review of the literature. We performed literature searches with PubMed from January 1990 to November 2020 using the keywords "rosacea", "pathogenesis", "ultraviolet radiation", "exposome", "photoprotection", "sunscreens" and "non-pharmacologic agents". The search was limited to English, Spanish, and French language articles.

Results: Several environmental factors such as UV light, diverse microorganisms, air pollution, tobacco smoking, nutrition, and psychological stress showed to trigger or worsen rosacea. UV radiation was reported to induce pro-inflammatory, pro-angiogenic, and pro-fibrotic responses. We found 6 original articles about the impact of sunscreens on rosacea. The use of sunscreens containing ingredients with emollient, anti-inflammatory, and/or vasoregulatory properties was shown to significantly improve symptomatology.

Conclusion: UV radiation and the exposome play a key role in the development of rosacea. UV light is implicated in all significant aspects of rosacea: skin inflammation, neoangiogenesis, telangiectasia, and fibrosis, and may even initiate rosacea. While the use of sunscreens is widely recommended, the literature on the impact of photoprotection in rosacea is scarce. Adequately formulated sunscreens could not only provide the required level of photoprotection, but may also help to mitigate the barrier dysfunction, neutralize facial redness (tinted sunscreens), and decrease inflammation and vascular dysfunction.

KEYWORDS
exposome, photoprotection, rosacea, sunscreens, ultraviolet radiation

1 | INTRODUCTION

Rosacea is a chronic, inflammatory skin disorder, which most frequently affects fair-skinned women. Rosacea prevalence can be highly variable, ranging from 1% to >20%. Rosacea is characterized by facial erythema, telangiectasia, erythematous papules, pustules, and flushing, among other manifestations. Patients complain about skin dryness, edema, stinging, itching, and burning sensations,[1] along with embarrassment and impairment of social life. Rosacea can produce a negative impact on quality of life and self-esteem.[2]

Pathophysiology of rosacea is not completely understood and involves a complex interaction among genetics, environmental factors, microorganisms, impaired skin barrier, neuronal and vascular dysfunction, and immune system disruption.[3] The exposome can be defined as the totality of environmental exposures in a lifetime, which can induce or modify diverse dermatoses.[4] The role of the exposome in rosacea must be highlighted: UV light, air pollution, tobacco smoking, nutrition, and psychological stress can trigger or worsen rosacea. Although UV exposure is one of the most commonly reported triggers and UV radiation can play a significant role in the pathogenesis of rosacea,[5] the literature on photoprotection in rosacea is relatively scarce. Furthermore, affected individuals typically react to diverse cosmetics and skincare products with stinging, burning, and worsening of rosacea.[6] While there is a wide range of available sunscreens, it can be difficult for patients and dermatologists to determine which sunscreens will be beneficial. The use of sunscreens containing ingredients with emollient, anti-inflammatory, and vasoregulatory properties could not only ensure the required level of photoprotection, but may also have the potential to mitigate the barrier dysfunction, neutralize facial redness (using green pigment as camouflage), and decrease inflammation and vascular dysfunction.

Here, we discuss the etiology of rosacea with emphasis on the role of UV radiation and the exposome, and review the importance of non-pharmacologic strategies with a focus on photoprotection.

2 | METHODS

We conducted a narrative review of the literature. We performed literature searches with PubMed from January 1990 to November 2020 using the keywords (non-MeSH) “rosacea”, “pathogenesis”, “ultraviolet radiation”, “exposome”, “photoprotection”, “sunscreens” and “non-pharmacologic agents”. The search was limited to English, Spanish, and French language articles. Articles were selected depending on their relevance.

3 | RESULTS AND DISCUSSIONS

3.1 | Pathophysiology of rosacea

Rosacea seems to develop from dysregulation of innate and adaptive immune systems and/or neurovascular dysfunction, disrupted skin barrier, and genetic predisposition. The exposome can play a significant role in inducing this impaired immune or neurovascular response.

3.1.1 | Genetic predisposition

The genetic contribution to the development of this disorder is estimated to be 46%.[7] Chang et al.[8] identified one single nucleotide polymorphism (rs763035) and three major histocompatibility complex class II alleles (HLA-DRB1*, HLA-DQB1*, and HLA-DQA1*) associated with rosacea.

3.1.2 | Microorganisms and the gut-skin axis

Recent evidence suggests a significant role of the cutaneous and gut microbiome. Small intestinal bacterial overgrowth, *Helicobacter pylori* infection, presence of b-hemolytic *Staphylococcus epidermidis*, and increased density of *Demodex folliculorum*, among other microorganisms, have been implicated in chronic skin inflammation and in the genesis of rosacea.[9]

3.1.3 | Impaired skin barrier

The lesional skin of rosacea patients can present lower skin conductivity, lower water content, and higher transepidermal water loss.[10] Impaired barrier function may promote skin bacterial colonization and inflammation.[10]

3.1.4 | Dysregulation of Immune response

Rosacea patients present higher levels of metalloproteinases (MMPs) and overexpression of Toll-like receptor 2 (TLR2). TLR2 activates the innate immune system in response to infection/infestation, such as the presence of *Demodex*.[3] Activation of the innate immune system leads to the release of pro-inflammatory cytokines and antimicrobial proteins such as cathelicidin. Cathelicidin is then cleaved into its active form, LL37, which induces degranulation of mast cells and secretion of multiple pro-inflammatory and pro-angiogenic molecules.[3]

3.1.5 | Neurovascular dysregulation

Activation of transient receptor potential (TRP) cation channels leads to the release of vasoregulatory neuropeptides calcitonin gene-related peptide and substance P. Both peptides can induce flushing. The TRP vanilloid 1 (TRPV1) is overexpressed in rosacea patients and is activated by heat, capsaicin, and inflammation. TRP ankyrin 1 (TRPA1) can be activated by cold, mustard oil, and formalin.[11]

3.1.6 | The exposome

As stated before, the exposome can be defined as the totality of environmental exposures of an individual in a lifetime and how those exposures relate to health. Herein, we will describe the most relevant exposome factors involved in the pathophysiology of rosacea.

The role of ultraviolet radiation

UV radiation is one of the most frequently reported triggers of rosacea.[2] The tendency of this disorder to affect the central face may be influenced by the exposure of convex surfaces of the face to UV light.[3] Sun-protected areas, such as the submental and supraorbital areas, are usually spared. Lifetime UV radiation exposure has been shown to be significantly associated with the presence of rosacea and is the single most important environmental variable.[7]

UVB radiation has significant angiogenic properties and can upregulate the expression of vascular endothelial growth factor, and increase endothelial cell proliferation within existing blood vessels, leading to telangiectasia and new blood vessels in animal models.[3] Chronic UVA exposure can induce MMP-1 overexpression, a metalloproteinase associated with dermal collagen degeneration in rosacea.[11]

UV irradiation can induce an imbalance between oxidant and antioxidant pathways, such as increased serum peroxide and decreased tissue superoxide dismutase observed in rosacea.[12] UV radiation produces reactive oxygen species (ROS), which can induce the release of pro-inflammatory cytokines by fibroblasts and keratinocytes. ROS levels are higher in patients with rosacea than in controls, and ROS can increase inflammatory response in these individuals.[11] UV irradiation can also induce endoplasmic reticulum stress leading to activation of TLR2, a mechanism through which UV could trigger innate immune responses in rosacea. Furthermore, UV irradiation may increase the expression of myeloid differentiation factor 88 (MyD88), an adaptor molecule for TLR signaling.[11]

Cathelicidin LL-37 contributes to enhanced photosensitivity in rosacea: It augments the pro-inflammatory and pro-angiogenic effects of UV radiation, increasing the release of IL-1β and augmenting the angiogenic potential of endothelial cells.[13] The link between UV radiation and the onset of inflammation mediated by the innate immune system has recently been described by Kulkarny et al.[5]: UVB induces keratinocyte damage, leading to the release of cathelicidin LL-37 and double-stranded RNA. This complex increases endothelial cell expression of adhesion molecules such as ICAM and VCAM, promoting an influx of neutrophils and monocytes into the dermis (Figure 1). These findings suggest that UV light can not only act as a trigger, but it may also initiate rosacea.

The contribution of visible light (VL) in the pathogenesis of rosacea needs to be addressed. We have not found studies on the role of VL in this dermatosis, although VL has been linked to diverse photoaggravated disorders such as melasma, postinflammatory hyperpigmentation, cutaneous porphyrias, and solar urticaria.[14] Furthermore, VL can trigger immediate erythema in light-skinned individuals, through a synergistic effect with UVA1.[15]

In summary, UV radiation is implicated in all key aspects of rosacea (Table 1): skin inflammation, neoangiogenesis, telangiectasia, and fibrosis.

Air pollution and smoking

The impact of air pollution on skin aging, pigmentation, and cutaneous diseases has been highlighted in recent years.[4] Outdoor air pollutants can be significantly associated with increased severity of symptoms in atopic dermatitis.[16] Traffic exhaust emissions seem to affect both skin barrier function and activation of immune responses.[16] UV light and air pollutants can have a synergic detrimental effect on the skin; this combination can induce significant cytotoxic and genotoxic damage.[4] While the impact of air pollution in rosacea remains to be determined, a recent study found a significantly increased risk of developing erythematous telangiectatic rosacea among smokers.[17] Volatile substances contained in cigarettes are likely to induce this erythematous condition (Table 2).[17]

It seems reasonable to advise patients to avoid ambient air pollutants when possible.

Nutrition

Regarding the impact of nutrition on rosacea, patients report certain foods as triggers such as spicy food (capsaicin), fatty food, those containing cinnamaldehyde (chocolate tomatoes and citrus[15]), alcohol, and hot beverages[18] as triggers.[19] Capsaicin and cinnamaldehyde can trigger TRP and promote vasodilation and flushing.[11] In contrast, increased coffee consumption seems to be inversely associated with the risk of incident rosacea, perhaps due to the high concentration of polyphenols found in coffee, which have antioxidant, anti-inflammatory, and vascular effects.[20]

Stress

Mental stress is one of the most frequently reported triggers by rosacea patients. Stress can increase the levels of corticosterone and the adrenocorticotropic hormone and activate the hypothalamic-pituitary-adrenal axis. Cortisol-releasing hormone (CRH) acts as a direct vasodilator and induces the degranulation of mast cells and the release of vasodilatory mediators, such as nitric oxide and histamine. CRH increases the levels of pro-inflammatory cytokines including IL-6, IL-8, and IL-18.[11] IL-8 impairs collagen production and stimulates the activity of MMP and epidermal water loss.[4] Mental stress can induce a hyper-responsiveness in sympathetic nerve activity in the supraorbital skin of rosacea patients and may cause neurovascular dysregulation and local inflammation.[11]

Heat

Heat is commonly reported as an exacerbating factor in rosacea. Individuals exposed to heat from using a tandoor oven exhibited

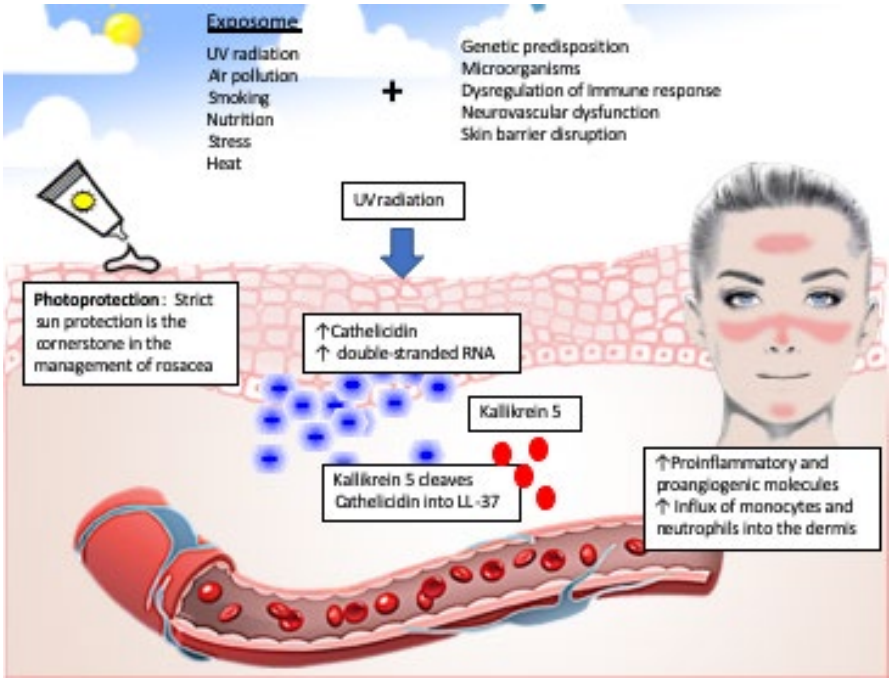

FIGURE 1 Role of ultraviolet radiation and exposome in the pathophysiology of rosacea. Pathophysiology of rosacea includes a complex interaction among genetics, ultraviolet light (UV), microorganisms, impaired skin barrier, neuronal and vascular dysfunction, and immune system disruptions. UVB radiation induces keratinocyte damage, leading to the release of cathelicidin LL-37 and double-stranded RNA. This complex increases endothelial cell expression of adhesion molecules, promoting an influx of neutrophils and monocytes into the dermis. Cathelicidin LL-37 also promotes angiogenesis, the release of pro-inflammatory cytokines and metalloproteinases, and leukocyte chemotaxis

TABLE 1 The role of ultraviolet radiation in the pathogenesis of rosacea

Epidemiological characteristics	UV radiation is one of the most frequently reported triggers of rosacea Lifetime UV radiation exposure is the single most important environmental variable associated with rosacea
Pro-angiogenic and pro-inflammatory effects	Augmented expression of VEGF, and increase endothelial cell proliferation within existing blood vessels Cathelicidin LL-37 augments the pro-inflammatory and pro-angiogenic effects of UV radiation, increasing the release of IL-1β and incrementing the angiogenic potential of endothelial cells
Activation of innate immune system	UVB radiation induces keratinocyte damage, leading to the release of cathelicidin LL-37 and double-stranded RNA. This complex increases endothelial cell expression of adhesion molecules such as ICAM and VCAM, promoting an influx of neutrophils and monocytes into the dermis
Induction of collagen dermal degeneration and fibrosis	Chronic UVA exposure can induce MMP-1 overexpression
Generation of reactive oxygen species	UV irradiation can induce an imbalance between oxidant and antioxidant pathways: increased serum peroxide and decreased tissue superoxide dismutase ROS levels are higher in patients with rosacea than in controls

Abbreviations: ICAM, intracellular adhesion molecule-1; IL, interleukin; MMP, metalloproteinase; ROS, reactive oxygen species; UV, ultraviolet; VEGF, vascular endothelial growth factor.

a significantly higher incidence of rosacea than control subjects.[21] Heat can activate TRPV1 and ankyrin 1, leading to vascular deregulation, flushing, and neurogenic leukocyte inflammation.[11]

3.2 | Non-pharmacologic treatment

3.2.1 | Cleansers

Recent evidence suggests that excessive cleansing can induce rosacea. High frequency of cleansing (more than once daily),[22,23] the usage of foaming cleansers,[23] a high quantity of cleansers,[22] long baths (≥11 min),[24] overuse of cleansing tool (more than four times/week),[22] daily exfoliating activity,[22] or sessions of deep cleansing treatment in beauty salons[22] presented a positive correlation with rosacea. Excessive cleansing may induce mechanical damage and chemical irritation to the stratum corneum and alter the normal cutaneous pH.[23]

As general skin care, the use of soap-free gentle facial cleansers, no more than once daily, must be encouraged.[23] As the skin barrier is already damaged in rosacea, any procedure or ingredient known to disrupt it should be avoided. Products containing ingredients likely

TABLE 2 Impact of the exposome on rosacea patients

Exposure	
UV radiation	Can exacerbate or initiate rosacea: Triggers the inflammasome Increases oxidative stress Induces vasodilation
Air pollution	UV light and air pollutants have a synergistic detrimental effect Induces significant cytotoxic and genotoxic damage
Tobacco smoking	Increased risk of developing rosacea
Nutrition	Triggers: alcohol, hot beverages, spicy food (capsaicin), fatty food, and those containing cinnamaldehyde such as chocolate, tomatoes, and citrus Protectors: increased coffee consumption
Psychological factors	Stress is a frequently reported trigger Can induce an hyper-responsiveness in sympathetic nerve activity in the supraorbital skin

to induce irritant or allergic contact dermatitis (camphor, menthol, eucalyptus oil, peppermint, witch hazel, or antiseptics) should not be recommended.[25]

3.2.2 | Moisturizers

Rosacea patients often suffer from dry facial skin, and non-oily moisturizers must be indicated. These products can repair the damaged skin barrier, relieve dry skin, improve skin homeostasis,[19,26] and may reduce the risk of rosacea onset.[23] Unfortunately, these individuals frequently report worsening of symptoms or heightened cutaneous sensitivity to skin care products, and allergic contact dermatitis is identified in 30% to 40% of cases.[27,28] This is why a skin care regimen should be as simple as possible, preferring cosmetically pleasing moisturizers without fragrance that have been developed to minimize the risk of irritant or allergic contact dermatitis.[23]

3.2.3 | Photoprotection

Strict sun protection is the cornerstone of management of rosacea. Daily use of a very high-tolerance broad-spectrum sunscreen with a minimum SPF of 30 is necessary.[1,29] Studies comparing the effects of different sunscreens on rosacea are lacking. Some authors recommend sunscreens containing physical or mineral filters with zinc oxide and/or titanium dioxide.[29] These physical sunscreens are usually well-tolerated, although patient adherence can be low, because some can leave a white layer on the skin after application. The selection of the texture of the sunscreen is relevant so as to ensure that the product is easy and gentle to apply and cosmetically acceptable. In facial care of rosacea, hydrophilic formulations such as water-based sunscreens are recommended more than oil-enriched formulations, which can lead to heat accumulation and a worsening of dermatosis. Additives such as emollients and/or ingredients with anti-inflammatory, skin-calming, or vessel-stabilizing properties should be considered.[6] Among these substances, dimethicone or Cyclomethicone can mitigate facial irritation.[25] Facial cosmeceuticals such as derivatives from *Ginkgo biloba*, *Aloe vera*, allantoin, feverfew, *Glycyrrhiza inflata*, and niacinamide have anti-inflammatory/antioxidant properties and can be useful in the treatment of rosacea[30] and may be added to sunscreen formulations. Topically applied polyphenols extracted from green tea or other plants present anti-inflammatory, antiangiogenic, and antioxidant properties. Polyphenols such as *Silybum marianum* (Silymarin), *Chrysanthemum indicum*, *Quassia amara* extract, and *Glycyrrhiza Inflata* root extract may be beneficial in reducing rosacea symptoms.[31] Topically applied kinetin (N^6-furfuryladenine), a plant cytokinin that may help to restore the skin barrier function, has demonstrated a beneficial effect in reducing erythema in mild-to-moderate rosacea.[32] Ectoine, a marine-derived molecule, is an effective long-term moisturizer, which prevents epidermal dehydration, reduces cutaneous inflammation, and protects DNA from damage by ionizing radiation,[33] and can be found in high-tolerance sunscreens.

We found six original articles about the impact of sunscreens on rosacea. A recent open-label study using a novel water-based sunscreen SPF 50+ containing two emollients found significantly less erythema, dryness, and scaling after 21 days of use. Subjects reported significantly less tension, dryness, and tickling.[34] A sunscreen containing sodium sulfacetamide 10% and sulfur 5% cream showed a greater percentage reduction in inflammatory lesions in a clinical trial compared with metronidazole 0.75% cream, as well as a significantly greater percentage of subjects with improved erythema.[35] A tinted daily SPF 30 facial moisturizer showed to improve the skin appearance and symptoms of skin dryness of rosacea-prone patients, reduced transepidermal water loss, and increased electrical capacitance.[36] A skin care regimen (cleanser, day care with SPF25 and night care) containing *Glycyrrhiza Inflata* root extract and 4-t-butylcyclohexanol was effective in improving signs of rosacea in patients with rosacea subtype I.[37] 4-t-butylcyclohexanol and *Glycyrrhiza Inflata* root extract can significantly reduce TRPV1 activation and prostaglandin E2 secretion, respectively.[38] An open-label study showed that the combination of UV filters together with cholesterol, trehalose, and ceramide, and anti-inflammatory ingredients

TABLE 3 Characteristics of recommended sunscreens in rosacea

Sun protection factor	Broad spectrum (≥SPF 30+)
Formula	High-tolerance water-based formula, easy to apply, and remove
Other active ingredients	Should contain ingredients with emollient, anti-inflammatory, skin barrier repair activity, or vasoregulatory properties
Color	Sunscreens containing green pigment should be considered as they can impact positively on patient appearance Tinted sunscreens containing formulations of iron oxides, pigmentary titanium dioxide, and zinc oxide can protect against visible light
Camouflage	Use of cosmetic camouflage with UV filters can give immediate satisfaction to patients and may reduce the impact of rosacea on quality of life

such as bisabolol, *Echinacea angustifolia* extract, *Boswellia serrate* resin extract, and esculin significantly reduced the erythema index and mean transepidermal water loss.[39] Tinted sunscreens using different concentrations of iron oxide, pigmentary titanium dioxide, and/or zinc oxide have shown to be effective in protecting against visible light.[14]

Cosmetic camouflage can be very important in patients with rosacea. Camouflage therapy can give immediate satisfaction to patients and may reduce the impact of the disease on the quality of life. The use of green pigment as an ingredient in sunscreens can also impact positively on patient appearance.[30]

The use of oral photoprotection has not yet been evaluated in rosacea. *Polypodium leucotomos* (PL) extract in combination with green tea polyphenols presents anti-inflammatory, anticarcinogenic, and antioxidant properties and has been used in photoaggravated dermatoses. This combination allows better tolerance to ultraviolet exposure and increases the minimal erythema dose,[40] and so might be an option for rosacea patients who have intolerance to sun exposure or engage in extensive outdoor activities.

In summary, topical sunscreens must be indicated for all rosacea patients, deciding which, however, among the vast range of products can be challenging. Products with broadband UV protection, water-based sunscreens, easy to remove, and containing ingredients with emollient, anti-inflammatory, antioxidant, and vasoregulatory properties should be preferred (Table 3). The use of tinted sunscreens or those containing green pigment for camouflage could be considered and discussed with the patient.

4 | CONCLUSION

The exposome can negatively impact on rosacea patients. Avoidance and/or protection (when possible) from known triggers such as environmental and emotional stimuli, and certain food should be recommended. Among these factors, UV radiation is crucial in the pathogenesis of rosacea. The appropriate skin care, use of moisturizers, and adequately formulated sunscreens are the cornerstone of treatment. Sunscreens can not only provide the required UV protection, but may also have the potential to moisturize the skin, repair the disrupted cutaneous barrier, reduce inflammation, and provide camouflage.

CONFLICT OF INTEREST

DM reported no conflict of interest, JP is a consultant for ISDIN, and CG and CT are employed by ISDIN who financed the publication expenses.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

We declare that this is an original and not previously published paper, and all contributions to the work are reported in the manuscript according to ICJME guidelines. There are no conflicts of interest to disclose.

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