Minireview

Aryl Hydrocarbon Receptor as a Therapeutical Target of Environmentally Induced Skin Conditions

Caroline de Almeida Freitas Accioli, Michelle Sabrina da Silva, Bianca Aloise Maneira Corrêa Santos, and Carlos Rangel Rodrigues

Laboratório de Planejamento Farmacêutico e Simulação Computacional (LaPFarSC) (C.d.A.F.A., B.A.M.C.S.) and Laboratório de Modelagem Molecular & QSAR-3D (ModMolQSAR), Departamento de Fármacos e Medicamentos (DEFARMED) (C.R.R.), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil and MEDCINVITRO, São Paulo, Brazil (M.S.d.S.)

ABSTRACT

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor, expressed in several tissues and involved in the response to environmental stressors. Studies have already associated exposure to environmental factors, such as organic air pollutants, products of the skin microbiota, and solar radiation, with the development/worsening of skin conditions, mediated by AhR. On the other hand, recent studies have shown that synthetic and natural compounds are able to modulate the activation of some AhR signaling pathways, minimizing the harmful response of these environmental stressors in the skin. Thus, AhR constitutes a new therapeutic target for the prevention or treatment of skin conditions induced by the skin exposome. Herein, an overview of potential AhR ligands and their biologic effects in environmentally induced skin conditions are presented. The literature survey pointed out divergences in the mechanism of action from a therapeutic perspective. Although most studies point to the benefits of ligand downregulation of AhR signaling, counteracting the toxic effects of environmental factors on the skin, some studies suggest the AhR ligand activation as a therapeutical mechanism for some skin conditions. Furthermore, both agonist and antagonist profiles were identified in the AhR modulation by the synthetic and natural compounds raised. Despite that, this target is still little explored, and further studies are needed to elucidate the molecular mechanisms involved and identify new AhR ligands with therapeutic potential.

SIGNIFICANCE STATEMENT

The aryl hydrocarbon receptor (AhR) is involved in different skin physiological and pathological processes, including toxic mechanisms of environmental factors. Synthetic and natural AhR ligands have demonstrated therapeutic potential for skin conditions induced by these agents. Thus, a comprehensive understanding of the skin toxicity mechanisms involving the AhR, as well as the use of AhR modulators from a therapeutic perspective, provides an alternative approach to the development of new treatments for skin disorders induced by the exposome.

Introduction

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor composed of multiple functional domains that plays a key role in the response to environmental aggressors (Soshilov and Denison, 2014; Esser and Rannug, 2015; Vogeley et al., 2019). In humans, it is expressed in several tissues, mainly in barrier organs, such as the skin, intestines, and lungs (Esser and Rannug, 2015).

The skin is a barrier organ constantly affected by environmental factors (Krutmann et al., 2021). Some authors have defined "skin exposome" as the total environmental exposures an individual undergoes throughout life that can induce or modify skin conditions (Krutmann et al., 2017a; Passeron et al., 2020). Among the exposome factors are organic air pollution, UV radiation (UVR), and the skin microbiome (through its metabolites) (Furue et al., 2014; Vogeley et al., 2019).

ABBREVIATIONS: AD, atopic dermatitis; AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; BaP, benzo[a]pyrene; BDDI, E/Z-2-Benzylidene-5, 6-Dimethoxy-3, 3-Dimethylindan-1-one; COX-2, cyclooxygenase 2; c-Src, proto-oncogene tyrosine-protein kinase c-Src; CYP1A1, cytochrome P450 1A1; EGCG, epigallocatechin gallate; FICZ, 6-formylindole [3, 2-b] carbazole; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor κ B; Nrf2, nuclear factor erythroid 2–related factor 2; PAS, Per-Arnt-Sim; PGE-2, prostaglandin E2; PM, particulate matter; ROS, reactive oxygen species; SAhRM, selective AhR modulators; TCDD, 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin; UVR, UV radiation; XRE, xenobiotic responsive element.
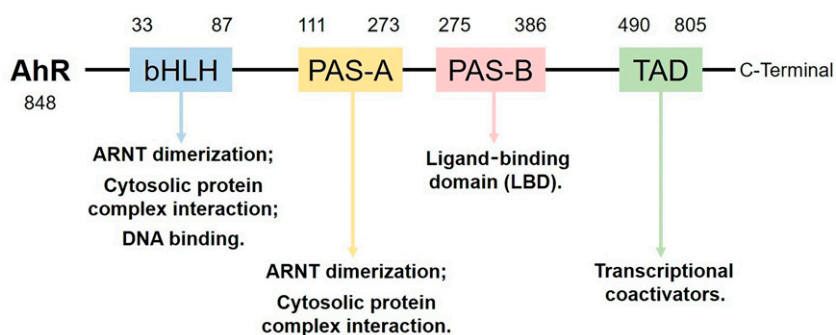
Fig. 1. Functional structure of AhR containing a basic helix-loop-helix (bHLH) domain, Per-ARNT-Sim (PAS-A and PAS-B) domains, and transactivation domain (TAD), with their respective positions and functions. Numbers at the domain boundaries refer to the amino acids order.

Studies have shown that AhR is involved in the pathogenesis of several skin conditions, many of them induced by external factors (Haarmann-Stemmann et al., 2012; Napolitano and Patruno, 2018). On the other hand, recent works have shown that synthetic and natural compounds are able to modulate AhR activation, minimizing its harmful response to the skin (Tigges et al., 2014; Cernuda and Clement, 2021; Kim et al., 2019b; Zamarrón et al., 2019; Kallimanis et al., 2022).

AhR is a still poorly explored therapeutical target for the prevention or treatment of skin conditions, and further studies are needed to discover new ligands with therapeutic potential. Therefore, the present review provides an overview of the role of AhR in skin physiologic and pathologic processes, the toxic mechanism of exposome factors through the AhR pathway, and, finally, discusses the use of synthetic compounds and natural extracts that potentially modulate AhR activation as therapeutical alternatives for skin disorders induced by environmental factors.

The AhR and Its Mechanism of Ligand Activation

The existence of AhR was first suggested in research on the induction mechanism of the cytochrome P450 enzymes expression by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). These findings led to the hypothesis that cytochrome P450 1A1 (CYP1A1) induction could be mediated by a receptor responsible for dioxin recognition (Nebert, 2017).

The human AhR has 848 amino acids, containing a basic helix-loop-helix (bHLH) domain and two Per-Arnt-Sim (PAS) subdomains. The PAS-A is involved in aryl hydrocarbon receptor nuclear translocator (ARNT) dimerization and cytosolic complex interaction, whereas PAS-B is the ligand-binding domain (Haarmann-Stemmann et al., 2012). It also has a transactivation domain, responsible for the transcription coactivator interactions (Schulte et al., 2017). Figure 1 shows the functional domains of AhR with their respective chain position and function.

When inactive in the cytoplasm, AhR constitutes a multiprotein complex, responsible for maintaining the three-dimensional structure of the receptor, protecting it from degradation and allowing proper recognition by ligands (Esser and Rannug, 2015). Some studies have suggested that the proto-oncogene tyrosine-protein kinase c-Src (c-Src) would also be a component of the cytosolic complex, and upon AhR ligand activation, this enzyme would participate in the nongenomic signaling pathway (Rothhammer and Quintana, 2019; Vogeley et al., 2019).

This complex dissociates upon a ligand interaction (agonist), leading to conformational changes and migration of the ligand-AhR complex to the nucleus, carried by transportins, where it dimerizes with ARNT. Then, the AhR-ARNT structure binds to xenobiotic responsive elements (XREs) in the promoter of target genes (Bisson et al., 2009).

Among cellular responses resulting from the XREs activation, there is an increase in the expression of cytochrome P450 enzymes, especially CYP1A1 (Liu et al., 2020). As an effect of the increase in CYP1A1, we can mention the formation of reactive oxygen species (ROS) from metabolites of polycyclic aromatic hydrocarbons. These compounds can induce inflammatory mediators and direct DNA damage, which ultimately leads to carcinogenesis (Tsuji et al., 2011; Vogeley et al., 2019).

AhR has also been shown to interact with other transcription factors, including nuclear factor κ B (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2), and estrogen and androgen receptors, leading to disturbances in the AhR-independent genes expression. This mechanism is also known as the noncanonical pathway (Bock, 2019).

The AhR activation leads to a nongenomic response, triggering an inflammatory cascade initiated by the rapid cytosolic Ca^{2+} increase and activation of c-Src, which stimulates the epidermal growth factor receptor (EGFR) pathway, increasing cyclooxygenase-2 (COX-2) expression, with the consequent synthesis of prostaglandins (Esser and Rannug, 2015) as shown in Fig. 2. The relationship between AhR activation and the induction of these markers was proven by studies with AhR-deficient mice exposed to AhR ligands. The expression of CYP1A1 and COX-2 was shown to be reduced (Fritsche et al., 2007).

Some ligands can bind to the PAS-B domain, leading to different conformational changes in protein structure and triggering distinct responses. After an antagonist binding, for example, the receptor remains inactive in the cytoplasm (Soshilov and Denison, 2014).

It should be noted that an antagonist does not exclude the AhR physiologic role; therefore, the antagonist-receptor complex is not the same as the AhR absence. The antagonist is unlikely to disturb the AhR cytosolic protein complex, which has physiologic importance (Smith et al., 2011).

Despite having been initially identified as a transcription factor that mediates xenobiotics toxicity, AhR exhibit a highly complex role, being involved in several physiologic and pathologic processes. Although its knowledge has expanded in recent years, there is still much to be elucidated about its signaling and ligand modulation (Esser et al., 2018).
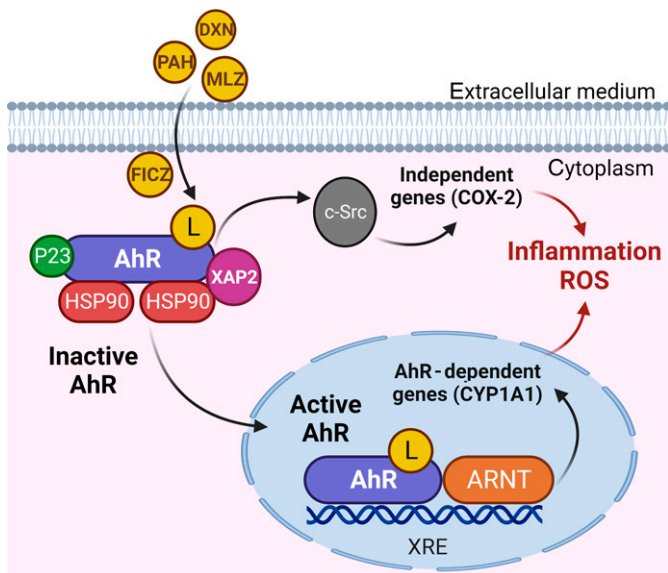
Fig. 2. Simplified representation of intracellular AhR signaling. Upon interaction with an agonist ligand, the receptor detaches from the cytoplasmatic protein complex, translocates to the nucleus, and dimerizes with ARNT, binding to XREs, thus promoting transcription of target genes, such as CYP1A1. AhR ligand activation also triggers c-Src tyrosine kinase signaling, leading to the expression of independent AhR genes, such as COX-2. Together, these signals promote oxidative stress and inflammation, among other responses. DXN, dioxin; HSP90, 90-kDa heat shock protein; MLZ, malassezin; P23, P23 cochaperone; PAH, polycyclic aromatic hydrocarbon; XAP2, X-associated protein 2.
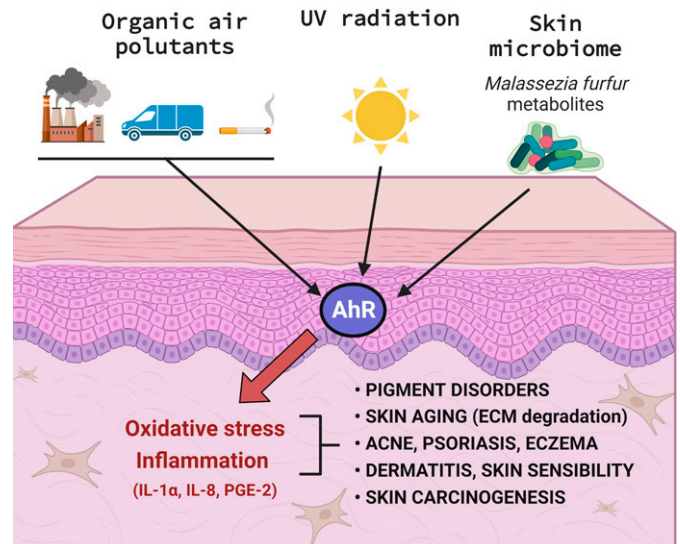

Fig. 3. Summary of external factors that activate the AhR pathway and the potential consequences of this activation in the skin. Organic air pollutants, UV radiation, and cutaneous microbiota metabolites may induce oxidative stress and inflammatory responses in the skin through activation of the AhR pathway. It may lead to pigment disorders; skin aging; and aggravation of inflammatory conditions such as acne, atopic dermatitis, psoriasis, and sensibility, as well as skin carcinogenesis process.

Role of AhR in Skin Physiologic and Pathologic Processes

In the skin, the AhR activation constitutes a common mechanism of action for several environmental factors. AhR ligands can originate from airborne particulate matter, from skin microbiota metabolites, or can also be formed in situ from UV radiation (Esser and Rannug, 2015). AhR signaling in the skin interferes with barrier function, cell differentiation, and skin pigmentation, in addition to mediating oxidative and inflammatory stress, which leads to other harmful effects (Esser and Rannug, 2015; Schalka et al., 2022).

All skin cell types express the AhR and, therefore, may respond to environmental or endogenous ligands. These ligands can affect AhR activity in the skin not only through topical exposure but also systemically (Vogeley et al., 2019). Figure 3 summarizes the environmental factors that impact the skin via AhR and the potential consequences of this pathway activation. AhR induces oxidative stress and inflammatory responses, which can negatively affect the skin, resulting in pigmentation disorders; skin aging due to the degradation of extracellular matrix elements; and aggravation of inflammatory conditions such as acne, psoriasis, eczema, dermatitis, and skin sensitivity, and even promotes cutaneous carcinogenesis (Richard et al., 2019; Vogeley et al., 2019).

The diversity of AhR-mediated responses in different skin cells makes it an interesting therapeutical target that is being increasingly investigated (Haarmann-stemmann et al., 2015; Napolitano and Patruno, 2018).

External Factors That Activate the AhR Pathway

Organic Air Pollutants. According to the World Health Organization, about 92% of the world's population lives in cities with air pollution levels above adequate health limits (https://www.who.int/news/item/27-09-2016-who-releases-country-estimates-on-air-pollution-exposure-and-health-impact).

Air pollutants can be classified into particulate matter (PM) and gases. Particulate matter can be divided according to the particle diameter into coarse particles, PM 10 (between 10 and 2.5 μm); fine particles, PM 2.5 (between 2.5 and 0.1μm); and ultrafine particles, PM 0.1 (<0.1 μm), which is mostly composed of organic substances (Kim et al., 2016). The smaller the particle, the greater the risk to human health (Krutmann et al., 2014).

Among the organic substances that compose the particles, there are polycyclic aromatic hydrocarbons, such as benzo[a]pyrene (BaP), and persistent organic pollutants. The most studied persistent organic pollutants are dioxins, benzofurans, and polychlorinated biphenyls, also called dioxin-like (Mancebo and Wang, 2015). All of these pollutant classes have already been studied and demonstrated AhR ligand activity (Kampa and Castanas, 2008).

Several studies have demonstrated the deleterious effects of these organic pollutants on the skin, impacting health and quality of life (Krutmann et al., 2014; Mancebo and Wang, 2015; Kim et al., 2016). Pollutants affect the incidence of inflammatory diseases such as atopic dermatitis, skin sensitivity (Hidaka et al., 2017), and acne (Krutmann et al., 2017b; Dréno et al., 2018; Liu et al., 2018); pigmentation disorders (Nakamura et al., 2015; Hüls et al., 2016; Grether-Beck et al., 2018); and skin aging (Krutmann et al., 2017a; Krutmann et al., 2021), and also the development of skin cancer (Baudouin et al., 2002; Vogeley et al., 2019).

Despite the fact that high acute exposure to organic pollutants causes marked damage to the skin, chronic exposure to environmental levels of these ligands also exhibits deleterious effects on the skin as described in epidemiologic studies (Hüls et al., 2016; Liu et al., 2018).

TCDD-exposed melanocytes showed a raised melanin content due to increased tyrosinase and tyrosinase-related protein-2 [(TYRP-2); or dopachrome tautomerase (DCT)] expression, indicating that AhR can modulate melanogenesis (Luecke et al., 2010). This helps to explain the hyperpigmentation seen in individuals after high exposure to organic pollutants as evidenced in dioxin accidents (Furue and Tsuji, 2019; Vogeley et al., 2019). A large epidemiologic study has linked this effect on melanocytes to normal exposure conditions, noting the correlation between exposure to traffic pollutants and lentigo formation in Caucasians and Asians (Hüls et al., 2016).

Environmental pollutants also trigger cellular oxidative stress in the skin via AhR activation (Richard et al., 2019). The CYP1A1 enzyme overexpressed by active AhR can lead to the generation of ROS and toxic metabolites such as 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE), a BaP metabolite that can form DNA adducts, promoting mutations (Richard et al., 2019). ROS accumulation in cells also causes DNA damage and immune system disruption and triggers an inflammatory cascade (Rothhammer and Quintana, 2019; Vogeley et al., 2019).

Cutaneous oxidative stress also increases the expression of matrix metalloproteinases (MMPs) that degrade collagen, thus leading to skin aging. ROS activates the signaling pathway of mitogen-activated protein kinases (MAPKs), inducing several transcription factors, such as NF-κB and activator protein 1 (AP-1). As a result, there is an increase in the synthesis of MMPs, mainly MMP-1, MMP-2, MMP-3, and MMP-9 (Tsai et al., 2014).

Furthermore, AhR signaling by pollutants triggers inflammatory cascades, leading to an increase in COX-2 and cytokines such as tumor necrosis factor-α (TNF-α), IL-1α, IL-8, and prostaglandin E2 (PGE-2) (Kim et al., 2016). A study showed that BaP promotes a dose-dependent increase in ROS and IL-8 in keratinocytes, and AhR silencing reduces these markers induced by BaP, indicating that this response involves the AhR receptor (Tsuji et al., 2011).

In vitro (human keratinocytes) and in vivo (mice) studies have shown that exposure of keratinocytes to particulate matter (PM 10) leads to increased COX-2 expression and PGE-2 synthesis, as well as reduced levels of filaggrin, disrupting the skin barrier. They also showed that pretreatment with an AhR antagonist had a protective effect against these changes (Lee et al., 2016).

The impact of air pollution on atopic dermatitis (AD) was also investigated. The artemin gene, responsible for epidermal hyperinnervation (hypersensitivity to pruritus), has been shown as an AhR target gene. Epidermal levels of CYP1A1 and artemin were significantly higher in atopic patients compared with healthy patients (Furue, 2020). Therefore, pollutants may exacerbate AD symptoms by direct activation of AhR (Hidaka et al., 2017; Furue, 2020).

UV Radiation. Solar radiation is known to be one of the main causes of skin damage. The mechanism of this damage varies from direct action on DNA to the formation of ROS, causing oxidative stress (Passeron et al., 2020).

UV radiation mechanism of action was initially demonstrated in studies with rats, where tryptophan photoproducts showed high AhR affinity. Subsequently, the chemical structure of the photoproducts 6,12-di-formyl indole [3,2-b] carbazole and 6-formyl indole [3,2-b] carbazole (FICZ) were identified. In 2007, FICZ formation was observed in UVB-irradiated keratinocytes, leading to both genomic and cytoplasmatic AhR responses, with CYP1A1 increase, and c-Src, EGFR and MAPK signaling that subsequently leads to COX-2 increase (Fritsche et al., 2007). A mouse study confirmed this UVB-induced signaling, showing the impairment of the response to UV radiation in AhR knockout animals (Rannug, 2010).

Recently, it was also observed that FICZ, on a nanomolar level, enhances the UVA-induced oxidative stress in the skin, demonstrating its photosensitizing action on keratinocytes associated with UVA, which results in DNA damage and cell death (Park et al., 2015). Thus, in addition to being generated in situ from UVB radiation, FICZ acts synergistically with UVA radiation, enhancing epidermal oxidative stress.

The involvement of AhR in UVB-induced skin pigmentation was also studied. A study of UVB-exposed mice demonstrated significantly less pigmentation in AhR-deficient animals than in wild-type mice. AhR knockout animals also showed reduced tyrosinase activity in melanocytes but no change in melanogenic factors release by keratinocytes. It suggests that UVB melanogenesis induction mediated by AhR occurs directly on melanocytes (Jux et al., 2011).

Therefore, AhR is involved in UVR-induced modulation of different processes in the skin, such as oxidative stress, DNA damage, inflammation, melanogenesis, and apoptosis, thereby contributing to skin photocarcinogenesis between other outcomes (Fritsche et al., 2007; Jux et al., 2011; Szelest et al., 2021).

Skin Microbiome. Healthy human skin has its surface colonized by a diversity of microorganisms, which generally coexist harmoniously. The set of these microorganisms is known as the skin microbiome, and its composition varies according to pH, humidity, and sebum production. External factors such as lifestyle habits add to genetic predispositions, shaping the individual's skin microbiome (Polak-Witka et al., 2020).

Staphylococcus epidermidis is a gram-positive bacteria member of the human skin microbiota, which has been shown to play an important role in cutaneous innate defense. It has been reported that AhR is crucial for the *S. epidermidis*–mediated responses in keratinocytes, although it remains to be shown which compounds are released by *S. epidermidis* and if they directly bind to AhR (Rademacher et al., 2019).

Yu et al. (2019) reported that indole-3-aldehyde (IAId), a tryptophan-derived AhR ligand produced by the skin microbiome, attenuates AD-like dermatitis through the inhibition of thymic stromal lymphopoietin (TSLP) expression, an inflammatory cytokine overexpressed in keratinocytes of AD patients. Due to an imbalanced skin microbiome, a reduced level of IAId may lead to skin inflammation in AD patients. Thus, these results suggest that a deficiency of AhR ligands produced by the microbiome may influence inflammatory skin diseases such as AD (Yu et al., 2019).

Therefore, AhR seems not only to sense environmental toxins but also participates in skin-microbiome interactions, and understanding the molecular mechanism whereby commensal bacteria modulate host defense may provide novel strategies

for the prophylaxis or treatment of cutaneous skin conditions (Rademacher et al., 2019; Yu et al., 2019; Szelest et al., 2021).

Yeasts of the *Malassezia* genus are one of the only eukaryotic microorganisms belonging to the skin microbiome and can become pathogenic under specific conditions (Gaitanis et al., 2012). *Malassezia furfur* (formerly *Pityrosporum ovale*) is a lipid-dependent species associated with cutaneous pathologies such as pityriasis versicolor, seborrheic dermatitis, and psoriasis (Gaitanis et al., 2012; Mexia et al., 2016). *M. furfur* produces indole metabolites from L-tryptophan, with potent AhR agonist activity. This amino acid is strongly present in sweat, suggesting that these compounds are largely produced and released by the yeast on the colonized surfaces, especially the scalp (Furue et al., 2014).

The AhR involvement in *Malassezia*-induced skin diseases is supported by studies that detected active metabolites, such as malassezin, ptiriacitrin, ptiriazepin, indirubin, triptantrin, and FICZ, in *M. furfur* strains obtained from patients' skin samples (Mexia et al., 2016).

Indeed, metabolites such as malassezin and ptyriacitrin were identified in the skin of patients with seborrheic dermatitis and were virtually undetected in healthy subjects (Gaitanis et al., 2012). They have also been identified in *Malassezia*-containing pityriasis versicolor lesions. It has been shown that, in the presence of malassezin, melanocytes undergo apoptosis, which may explain the depigmented areas in this pathology (Krämer et al., 2005; Magiatis et al., 2013).

Regarding scalp psoriasis, the rate of *Malassezia*-positive cultures was higher in psoriatic patients compared with healthy subjects. Refractory scalp psoriasis successfully treated with imidazoles corroborates the role of *Malassezia* in the exacerbation of the disease (Polak-Witka et al., 2020). On the other hand, studies show improvement in psoriatic plaque treated with indigo naturalis (*Strobilanthes formosanus Moore*), which contains indole compounds indigo and indirubin, also produced by the yeast (Lin et al., 2008). *Malassezia* also seems to be involved in "head and neck" atopic dermatitis in adults who respond to antimycotic therapy and exhibit *Malassezia* antibodies circulating. Although the suggested mechanism does not involve AhR activation by metabolites, studies are needed to confirm or discard the AhR pathway involvement in inflammatory signaling (Vijaya Chandra et al., 2021).

Therefore, as AhR activation can trigger opposite responses, such as melanogenesis by TCDD and melanocyte apoptosis by malassezin, and the role of these indole microbiota metabolites on the AhR pathway is still not entirely clear. Further studies are needed to elucidate its mechanisms in cutaneous pathophysiology and to investigate the potential of AhR as a therapeutical target for pathologies associated with the skin microbiome.

AhR Modulation as a Therapeutic Target for Skin Conditions

The diversity of AhR-mediated responses from the binding of endogenous and exogenous compounds makes it a potential therapeutic target for cutaneous conditions (Napolitano and Patruno, 2018), immunologic diseases (Rothhammer and Quintana, 2019; Hui and Dai, 2020), and even cancer progression (Safe et al., 2017; Yang et al., 2019).

This has led to a growing search for effective and safe AhR modulators, although data are still contradictory regarding the positive effect of AhR activation/inhibition (Haarmann-Stemmann et al., 2012; Napolitano and Patruno, 2018).

Some synthetic and natural compounds are known to interact with AhR, leading to the inhibition of its genomic signaling and thus acting as antagonists. Currently, the most well accepted mechanism is that by competing with agonists for receptor interaction and opposing its cell signaling, these compounds minimize the negative impact of external factors mediated by AhR on the skin. In general, the use of AhR ligands aims to modulate receptor activation so that physiologic effects are maintained and toxic effects suppressed (Esser and Rannug, 2015).

AhR Modulation by Synthetic Compounds

So far, to our knowledge, there is only one synthetic compound developed for topical use targeting AhR modulation. E/Z-2-Benzylidene-5,6-Dimethoxy-3,3-Dimethylindan-1-one (BDDI), patented as SymUrban (Symrise, Holzminden, Germany), was tested on keratinocytes and in the skin of volunteers showing to be safe and effective in preventing AhR-mediated skin damage by pollutants and UV radiation (Tigges et al., 2014).

The compound was not cytotoxic in keratinocytes in the concentration range studied and showed a reduction in CYP1A1 expression induced by BaP, FICZ, or UVB with BDDI pretreatment in a concentration-dependent manner. It was observed that the BDDI pretreatment effect is temporary since it is effective before 1 hour but ineffective before 24 hours. It also showed effectiveness when applied after UVB irradiation, confirming its action as AhR modulation, not as a UVR filter. In addition, the coexposure to BDDI with TCDD or FICZ prevented the AhR binding to XREs, evidencing the BDDI activity as an AhR competitive antagonist (Tigges et al., 2014). Finally, the in vivo protective effect of a formulation containing 0.5% BDDI on UV-induced expression of CYP1A1, COX-2, and MMP-1 in the skin of healthy volunteers treated 4 days before irradiation was investigated. The formulation was able to prevent the increase of these markers induced by radiation, evidencing its potential for "antiphotopollution" cosmetic formulations (Tigges et al., 2014).

Some works investigated the action of other synthetic compounds in the modulation of AhR, suggesting a possible therapeutic potential, but they were not specifically tested in skin assays. An example is 2-methyl-2H-pyrazolo-3-carboxylic acid (2-methyl-4-o-tolylazo-phenyl)-amide (CH223191), a dioxin-selective AhR antagonist (Kim et al., 2006). Leflunomide, an anti-inflammatory drug used in the treatment of rheumatoid and psoriatic arthritis, exhibits an AhR agonist activity (O'Donnell et al., 2010). The 1-allyl-7-trifluoromethyl-1H-indazol-3-yl]-4-methoxy phenol (SGA 360) showed anti-inflammatory activity through selective modulation of the AhR (Murray et al., 2010). The N-(2-(1H-indol-3-yl)ethyl)-9-isopropyl-2-(5-methyl pyridin-3-yl)-9H-purin-6-amine (GNF351) was described as a "pure" nonselective antagonist (Smith et al., 2011). Recently, thiazolidinediones exhibited activity as AhR ligands (Liu et al., 2020).

These findings suggest that AhR modulation by synthetic substances, already approved for different purposes, constitutes a potential therapeutic strategy in several conditions, including the skin. The AhR-selective activation or inhibition is desired

according to the mechanism involving each disease. Thus, further studies may help to understand the molecular interaction of active compounds with AhR to characterize them as safe and effective AhR modulators to the skin.

AhR Modulation by Natural Compounds

Naturally occurring AhR ligands mainly belong to the general class of polyphenols (Xue et al., 2017; Yang et al., 2019). Studies on the different effects of polyphenols on the AhR modulation were extensively reviewed by Xue et al. (2017). Both agonist and antagonist actions were identified in these ligands, and both may be interesting from a therapeutic perspective, according to the pathology, evidencing the pathway complexity (Xue et al., 2017).

Recently, the potential of isolated natural compounds or polyphenol-rich extracts has been demonstrated in the modulation of several environmentally induced skin disorders as shown in the following studies.

Flavonoids. Flavonoids are a class of polyphenolic compounds derived from plant secondary metabolism whose health benefits, especially their antioxidant and anti-inflammatory activities, are widely recognized (Jin et al., 2018). Several components of this class, such as chrysin, luteolin, apigenin, quercetin, rutin, galangin, Baicalein, and Kaempferol, have already demonstrated AhR ligand activity (Xue et al., 2017; Jin et al., 2018; Goya-Jorge et al., 2021).

An example is eupafolin, a flavonoid obtained from *Phyla nodiflor* leaves, which has been shown to reduce inflammatory (COX-2 and PGE-2) and oxidative (ROS, NADPH oxidase) markers in pollutant-exposed keratinocytes. The study confirmed that topical treatment with eupafolin inhibits pollutant-induced COX-2 expression (Lee et al., 2016b). Although the authors did not suggest AhR as a molecular target of eupafolin, they have demonstrated that its anti-inflammatory effects are related to MAPK and NF-κB signaling reduction, which are pathways involved in the AhR activation (Kim et al., 2016).

Afzelin is a Kaempferol-derived flavonoid, from *Thesium chinense*, with anti-inflammatory, antibacterial, and anticancer properties described. Afzelin was able to inhibit the synthesis of IL-1α in particulate matter–exposed keratinocytes. This compound reduced ROS generation and p38 MAPK activation, and, once again, the AhR pathway was not addressed, although this is a possible afzelin mechanism of action (Kim et al., 2019a).

Green tea (*Camellia sinensis*) is another rich source of polyphenols that has been commercially used. Among its major components are epigallocatechin and epigallocatechin gallate (EGCG), which belong to the family of flavonoids (Boo, 2019). Previous studies have shown that both the extract and the isolated catechins are able to prevent AhR activation in vitro (Palermo et al., 2003). Recently, EGCG showed a protective effect against particulate matter–induced damage in keratinocytes, reducing ROS generation, and TNF-α, IL-1β, IL-6, IL-8 and MMP-1 expression (Seok et al., 2018). Another study has confirmed the EGCG protective effect on fibroblasts, also exposed to particulate matter, reducing MMPs and NF-κB expression via MAPKs and increasing cell viability (Wang et al., 2019). Such results have suggested EGCG as a potential antipollution active compound for topical use, and although it was not directly demonstrated by these studies, its mechanism of action may involve AhR modulation.

Stilbenes. Stilbenes are a class of polyphenols whose AhR activity has been investigated in skin conditions. Resveratrol is the best-known compound in the class, and its high antioxidant activity is recognized and widely used by the cosmetic industry (Ratz-Łyko and Arct, 2019).

Resveratrol reduced AhR activation and pollutant-induced ROS generation in keratinocytes, thus inhibiting subsequent responses through COX-2, PGE2, MMP-1, MMP-9, and IL-8 markers (Shin et al., 2020). In another study, resveratrol restored survival rates of pollution-exposed keratinocytes, reducing ROS and IL-6 levels. However, AhR involvement was not directly investigated (Boo, 2019). Previous studies have shown the protective effect of resveratrol in other tissues exposed to pollutants (BaP) by AhR pathway modulation (Revel et al., 2001, 2003).

Tapinarof (GSK289451) is a stilbene produced by an entomopathogenic nematode symbiotic bacteria, whose topical application was effective in the treatment of inflammatory skin conditions such as psoriasis and AD, both in preclinical and clinical studies (Smith et al., 2017; Peppers et al., 2019; Robbins et al., 2019). Tapinarof was able to control proinflammatory cytokine expression (such as IL-17A) in lymphocytes and skin explants and increases the expression of filaggrin, hornerin, and involucrin, involved in skin barrier function. It promotes AhR nuclear translocation in keratinocytes and increases CYP1A1 expression in skin explants and CD4$^+$ T cells in a dose-dependent manner. Such properties are AhR mediated since the compound potently interacts with the receptor compared with resveratrol, and tests with mice showed that Tapinarof was able to protect the skin from imiquimod-induced inflammation, but this effect was not observed in AhR knockout animals, confirming its mechanism of action (Smith et al., 2017).

Tapinarof also has antioxidant properties, as well as several polyphenols, and the ability to activate the Nrf2 pathway, which other AhR agonists (such as TCDD) cannot do, indicating that AhR/Nrf2 dual activation may be the key to the differential therapeutic role of AhR agonists such as tapinarof versus toxicants, such as organic pollutants (Smith et al., 2017).

In addition, other polyphenols have already been studied for AhR action in other cellular assays than the skin and, consequently, may also be promising in future investigations for cutaneous use. Among them are quercetin (Ramadass et al., 2003), harmaline and harmalol (El Gendy et al., 2012), Ginsenosides (Hu et al., 2013), curcumin and derivatives (Nakai et al., 2018), and others.

Natural Extracts. *Camellia japonica* flower extract has demonstrated a protective effect of pollutant-induced damage on fibroblasts, preventing MMP-1 expression and AhR activation, and also exhibits antioxidant activity. The extract was standardized in gallic acid, but the phenolic composition was not determined, so the extract efficacy was not attributable to the interaction of a specific AhR ligand (Kim et al., 2019b). Despite that, studies indicate that the extract contains flavonoids, such as quercetin and rutin, whose AhR modulation has already been reported (Xue et al., 2017; Boo, 2019).

Pycnogenol (Horphag Research, Geneva, Switzerland) is a standardized extract of the bark of *Pinus pinaster*, mainly composed of catechin and epicatechin, indicating that its mechanism of action on the skin may occur through

TABLE 1
Overview of potential AhR ligands and their biologic effects in environmentally induced skin conditions

Compound	Experimental Model	Biologic Result	Ref
Synthetic Compound			
BDDI	Keratinocytes (NHEK); keratinocytes (HaCaT); human skin Biopsies (in vivo Topical treatment).	Reduction of BaP-, FICZ-, and UVB-induced CYP1A1 expression in a dose-dependent manner; BDDI coexposure with TCDD or FICZ prevented AhR/ARNT binding to XREs; In vivo reduction of UVB-induced expression of CYP1A1, COX-2, and MMP-1.	Tigges et al., 2014
Natural compounds			
Eupafolin	Keratinocytes (HaCaT); Topical treatment of BALB/c nude mice (in vivo).	Inhibition of PM-induced intracellular ROS, NADPH oxidase activity, COX-2 and PGE2 expression, and MAPK and NK-κB activation; In vivo inhibition of COX-2 expression in PM-treated mice.	Lee et al., 2016a
Afzelin	keratinocytes (HaCaT);	Inhibition of PM-induced intracellular ROS, p38 MAPK, AP-1 activation, and IL-1α expression.	Kim et al., 2019a
EGCG	Primary human epidermal keratinocytes	Inhibition of PM-induced intracellular ROS, and TNF-α, IL-1β, IL-6, IL-8 and MMP-1 expression.	Seok et al., 2018
	Human dermal fibroblasts (HDF)	Increase of cell viability and reduction of PM-induced MMP expression and NF-κB and MAPKs activation.	Wang et al., 2019
Resveratrol	Keratinocytes (NHEK)	Inhibition of PM-induced intracellular ROS and COX-2, PGE-2, MMP-1, MMP-9, and IL-8 expression	Shin et al., 2020
	Keratinocytes (HaCaT) 3D skin model	Inhibition of PM-induced intracellular ROS and IL-6 expression. Restored survival rates of PM-exposed keratinocytes.	Boo, 2019
Tapinarof (GSK289451)	Skin-resident immune cell (from human skin explants); keratinocytes (HaCaT); imiquimod-treated mice (psoriasis model)	Induction of CYP1A1 expression in CD4$^+$ T cells and induction of nuclear translocation of AhR/ARNT in HaCaT cells, both in a dose-dependent manner. Induction of filaggrin, hornerin, and involucrin expression in keratinocytes. Reduction of imiquimod-induced inflammatory cytokines. Reduction of IL-17A levels in vitro, ex vivo, and in IMQ-treated mice.	Smith et al., 2017
Natural extracts			
C. japonica flower extract	Keratinocytes (NHDF) Human skin explants (ex vivo)	Inhibition of pollutant-induced XRE activity and CYP1A1 expression and reduction of intracellular ROS and MMP-1 expression in NHDFs; Reduction of pyknotic nuclei cells and MDA levels, prevention of DEJ detachment, and improvement of ECM density in urban pollutant-exposed skin explants.	Kim et al., 2019b
D. antarctica extract	Queratinócitos (HaCaT) fibroblastos (HDF)	Reduces UV-induced cellular death. Inhibits TCDD-induced nuclear translocation of AhR and increases loricrin synthesis in keratinocytes.	Zamarrón et al., 2019
D. antarctica extract (Edafence)	Clinical study (topical formulation)	Improvement of the skin appearance and barrier function and reduction of TEWL and lipid peroxidation in individuals under high air pollution conditions.	Mataix et al., 2020

TABLE 1 continued

Compound	Experimental Model	Biologic Result	Ref
R. officinalis, *O.Europaea, L. citriodora,* and *S.japonica* leaf extracts (Zeropollution)	Keratinocytes (HaCaT), Human skin explants (ex vivo)	Reduction of intracellular ROS in keratinocytes exposed to UV and urban dust (pollutants). Reduction of pollutant-induced MDA and IL-1α levels and AhR activation in skin explants.	Cernuda and Clement, 2021
	Clinical study (oral supplementation)	Improvement of elasticity, firmness, and skin moisturization and decrease of wrinkle depth, TEWL, and dark spots pigmentation in Caucasian and Asian individuals exposed to air pollution.	Nobile et al., 2021
Pycnogenol (extract of *P. pinaster*)	Clinical study (oral supplementation)	Prevention of skin dehydration, TEWL, and skin darkening and improvement of viscoelastic properties in outdoor workers under high air pollution conditions	Zhao et al., 2021
R. officinalis leaf extract	Spontaneous immortalized keratinocytes (SIK 28)	The extract inhibits AhR activation by TCDD and *Malassezia* metabolites (FICZ, indirubin, and pityriazepin) in human keratinocytes.	Kallimanis et al., 2022

AP-1, activator protein 1; DEJ, dermal epidermal junction; ECM, extracellular matrix element; HaCaT, human keratinocyte cells; IMQ, imiquimod; MDA, malondial-dehyde; NHDF, normal human dermal fibroblast; NHEK, normal human epidermal keratinocytes; TEWL, transepidermal water loss; TNF-α, tumor necrosis factor-α.

AhR modulation. Among the main effects of Pycnogenol supplementation are the prevention of UV damage, regulation of skin pigmentation, and improvement of extracellular matrix elements and barrier function (Grether-Beck et al., 2016). A clinical study has shown that daily oral intake of Pycnogenol for 12 weeks benefits the skin of Chinese outdoor workers highly exposed to particulate matter. It prevents transepidermal water loss and skin darkening and improves viscoelastic properties. These effects were not seen in the placebo-treated group (Zhao et al., 2021).

Deschampsia antarctica is an Antarctica-native grass whose aqueous extract has shown photoprotective and antioxidant activity. This is partly due to photostabilizing compounds, dehydrins, and phenolics, such as luteolin and apigenin. (Mataix et al., 2020). The protective effect of the commercial extract (Edafence Cantabria Laboratories, Madrid, Spain) was investigated on keratinocytes and fibroblasts exposed to UVA, UVB, and TCDD. The extract attenuated UV-induced DNA damage and proapoptotic signaling. In addition, it prevented the AhR activation and loricrin reduction by TCDD (Zamarrón et al., 2019). Clinical studies of cosmetic formulations containing *D. antarctica* extract have also been conducted under relatively high air pollution conditions, in which a reduction of transepidermal water loss, a decrease in lipid peroxidation, and improvement in the barrier function and skin appearance were observed. Together, these results suggest the potential of the extract in skin protection against environmental stressors, both for its antioxidant activity and AhR modulation ability (Mataix et al., 2020).

The food supplement Zeropollution (Monteloeder S.L, Alicante, Spain) is a blend of four natural extracts that promote ROS reduction in UV and pollutants concomitantly exposed keratinocytes. In a study with pollutant-exposed skin explants, the supplement reduced malondialdehyde (MDA) levels, a marker of oxidative stress, IL-1α expression, and the AhR activation decrease (Cernuda and Clement, 2021). The supplement extracts are polyphenol-rich, with a minimum content of some compounds: *Rosmarinus officinalis* leaf extract standardized at 4.5% carnosic acid plus carnosol, *Olea Europaea* leaf extract standardized at 4.5% oleuropein and 1.5% hydroxytyrosol, *Lippia citriodora* leaf extract standardized at 6.5% verbascoside, and *Sophora japonica* extract standardized at 3.5% quercetin (Cernuda and Clement, 2021). In a clinical study with pollution-exposed Caucasian and Asian individuals treated with the supplement, an improvement in different skin parameters was observed, such as decreased wrinkles and dark spots, increased elasticity and firmness, and an improvement in skin hydration. Both intergroup and intragroup analyses indicate that the treatment improved all parameters in both studied populations, neutralizing the pollution skin damage, also by oral use (Nobile et al., 2021).

Recently, *R. officinalis* leaf extracts were investigated as AhR antagonists through different cellular models. Methanolic extract inhibits AhR activation by TCDD, FICZ, indirubin, and pityriazepin in human keratinocytes, supporting its potential use for skin protection against environmental pollutants, UV radiation, and *Malassezia* metabolites. Despite that, in vivo studies are needed to confirm this effect (Kallimanis et al., 2022). An overview of the studies of potential AhR ligands in skin conditions is provided (Table 1).

Discussion

The skin is continuously exposed to several environmental aggressors, such as UV radiation, airborne particulate matter (containing organic pollutants), and skin microbiota metabolites. The search for alternatives to prevent skin damage induced by the exposome is increasing. Studies on environmental stressors' damage exhibit the AhR activation as a common mechanism. Therefore, the modulation of AhR activation constitutes an interesting therapeutical alternative, although still poorly explored in cosmetics.

Considering that the work focuses on AhR as a target for skin conditions induced by environmental factors, the control of receptor superactivation by these aggressors is suggested as the desired mechanism. Thus, the use of antagonists or

partial agonists as competitor ligands constitutes the main strategy of AhR modulation against skin exposome damage. On the other hand, the study of Smith et al. (2017) proposes AhR agonism as a therapeutic mechanism for inflammatory cutaneous conditions, such as psoriasis and AD. The authors suggest that the AhR/Nrf2 dual activation triggers antioxidant and immunomodulatory responses on the skin and immune cell types, which leads to an anti-inflammatory effect and improvement of barrier function, which are unbalanced in these pathologies, as the key to the differential therapeutic role of these agonists compared with toxicant agonists. It is worth highlighting the differences in this study since the investigated compound was not exposed together to environmental xenobiotics and thus was not able to identify its possible activity in counteracting these aggressions.

Furthermore, it is important to understand the differences and similarities between selective AhR modulators (SAhRM) and AhR antagonists in a particular biologic context. If the aim is blocking an XRE-mediated toxic response such as the induction of inflammatory cytokines, both an antagonist and an SAhRM may exhibit the same inhibitory activity. However, if the goal were to block all direct AhR-mediated events, an AhR antagonist and a SAhRM would produce very different outputs. Thus, the suitable alternative depends on what you want to modulate, and the definition of agonist and antagonist for AhR ligands has been questioned in literature, proposing "modulator" as the appropriate term (Dolciami et al., 2020).

The discussed studies have shown the protective effect of synthetic and natural compounds against environmentally induced damage in the skin, either by biochemical markers or by clinical parameters. However, most do not investigate the molecular mechanism of this effect; hence, further studies are needed to confirm the AhR involvement and specific ligand-binding modes that leads to differential AhR signaling, supporting the search for new safe and effective AhR modulators for cutaneous application.

Regarding synthetic compounds, considering that several drugs approved for other purposes also act on AhR, it is interesting to investigate them in cutaneous models, to support its approval for use in topical products, since this represents less time and cost-development strategy.

Concerning natural compounds, most of the studies investigated extracts' efficacy, with uncharacterized phytochemical profiles, and unstudied isolated compounds, making it difficult to correlate their effects with the AhR pathway. Moreover, the patentability limitation of natural compounds perhaps decreases their industrial interest in drug development (Hui and Dai, 2020). On the other hand, consumer interest in natural products and the growing relevance of sustainability in the development of pharmaceutical and cosmetic formulations make natural sources more attractive.

Synthetic and natural ligands, as well as plant extracts, have demonstrated therapeutic potential for skin conditions induced by external stressors. Thus, this review provides a comprehensive understanding of the skin toxicity mechanism of external factors involving the AhR, as well as compounds with preventive efficacy described. It also emphasizes the necessity of more investigations of AhR modulation mechanisms, elucidating the mode of action of these compounds, being useful for future studies of AhR ligands as active ingredients for topical formulations.

References

Baudouin C, Charveron M, Tarroux R, and Gall Y (2002) Environmental pollutants and skin cancer. *Cell Biol Toxicol* **18**:341–348.

Bisson WH, Koch DC, O'Donnell EF, Khalil SM, Kerkvliet NI, Tanguay RL, Abagyan R, and Kolluri SK (2009) Modeling of the aryl hydrocarbon receptor (AhR) ligand binding domain and its utility in virtual ligand screening to predict new AhR ligands. *J Med Chem* **52**:5635–5641.

Bock KW (2019) Aryl hydrocarbon receptor (AHR): From selected human target genes and crosstalk with transcription factors to multiple AHR functions. *Biochem Pharmacol* **168**:65–70.

Boo YC (2019) Can plant phenolic compounds protect the skin from airborne particulate matter? *Antioxidants* **8**:379.

Cernuda NC and Clement AP (2021) Composition comprising vegetable extracts with flavonoids for alleviating the many effects of air pollution on the skin. European Patent EP 3 811 926 A1. 2021 Apr 28.

Dolciami D, Ballarotto M, Gargaro M, López-Cara LC, Fallarino F, and Macchiarulo A (2020) Targeting Aryl hydrocarbon receptor for next-generation immunotherapies: Selective modulators (SAhRMs) versus rapidly metabolized ligands (RMAhRLs). *Eur J Med Chem* **185**:111842.

Dréno B, Bettoli V, Araviiskaia E, Sanchez Viera M, and Bouloc A (2018) The influence of exposome on acne. *J Eur Acad Dermatol Venereol* **32**:812–819.

Esser C, Lawrence BP, Sherr DH, Perdew GH, Puga A, Barouki R, and Coumoul X (2018) Old Receptor, New Tricks-The Ever-Expanding Universe of Aryl Hydrocarbon Receptor Functions. Report from the 4th AHR Meeting, 29–31 August 2018 in Paris, France. *Int J Mol Sci* **19**:3603.

Esser C and Rannug A (2015) The aryl hydrocarbon receptor in barrier organ physiology, immunology, and toxicology. *Pharmacol Rev* **67**:259–279.

Fritsche E, Schäfer C, Calles C, Bernsmann T, Bernshausen T, Wurm M, Hübenthal U, Cline JE, Hajimiragha H, Schroeder P, et al. (2007) Lightening up the UV response by identification of the arylhydrocarbon receptor as a cytoplasmatic target for ultraviolet B radiation. *Proc Natl Acad Sci USA* **104**:8851–8856.

Furue M (2020) Regulation of filaggrin, loricrin, and involucrin by IL-4, IL-13, IL-17A, IL-22, AHR, and NRF2: Pathogenic implications in atopic dermatitis. *Int J Mol Sci* **21**:1–25.

Furue M, Takahara M, Nakahara T, and Uchi H (2014) Role of AhR/ARNT system in skin homeostasis. *Arch Dermatol Res* **306**:769–779.

Furue M and Tsuji G (2019) Chloracne and hyperpigmentation caused by exposure to hazardous aryl hydrocarbon receptor ligands. *Int J Environ Res Public Health* **16**:4864.

Gaitanis G, Magiatis P, Hantschke M, Bassukas ID, and Velegraki A (2012) The Malassezia genus in skin and systemic diseases. *Clin Microbiol Rev* **25**:106–141.

El Gendy MAM, Soshilov AA, Denison MS, and El-Kadi AO (2012) Harmaline and harmalol inhibit the carcinogen-activating enzyme CYP1A1 via transcriptional and posttranslational mechanisms. *Food Chem Toxicol* **50**:353–362.

Goya-Jorge E, Jorge Rodríguez ME, Veitía MSI, and Giner RM (2021) Plant occurring flavonoids as modulators of the aryl hydrocarbon receptor. *Molecules* **26**:2315.

Grether-Beck S, Marini A, Jaenicke T, Brenden H, Uthe I, Felsner I, and Krutmann J (2018) 1209 Ambient relevant diesel exhaust particles cause skin hyperpigmentation ex vivo and in vivo in human skin: The Düsseldorf Pollution Patch Test. *J Invest Dermatol* **138**:S205.

Grether-Beck S, Marini A, Jaenicke T, and Krutmann J (2016) French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence. *Skin Pharmacol Physiol* **29**:13–17.

Haarmann-Stemmann T, Abel J, Fritsche E, and Krutmann J (2012) The AhR-Nrf2 pathway in keratinocytes: on the road to chemoprevention? *J Invest Dermatol* **132**:7–9.

Haarmann-Stemmann T, Esser C, and Krutmann J (2015) The Janus-Faced Role of Aryl Hydrocarbon Receptor Signaling in the Skin: Consequences for Prevention and Treatment of Skin Disorders. *J Invest Dermatol* **135**:2572–2576.

Hidaka T, Ogawa E, Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Fujimura T, Aiba S, Nakayama K, Okuyama R, et al. (2017) The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. *Nat Immunol* **18**:64–73.

Hu Q, He G, Zhao J, Soshilov A, Denison MS, Zhang A, Yin H, Fraccalvieri D, Bonati L, Xie Q, et al. (2013) Ginsenosides are novel naturally-occurring aryl hydrocarbon receptor ligands. *PLoS One* **8**:e66258.

Hui W and Dai Y (2020) Therapeutic potential of aryl hydrocarbon receptor ligands derived from natural products in rheumatoid arthritis. *Basic Clin Pharmacol Toxicol* **126**:469–474.

Hüls A, Vierkötter A, Gao W, Krämer U, Yang Y, Ding A, Stolz S, Matsui M, Kan H, Wang S, et al. (2016) Traffic-Related Air Pollution Contributes to Development of Facial Lentigines: Further Epidemiological Evidence from Caucasians and Asians. *J Invest Dermatol* **136**:1053–1056.

Jin UH, Park H, Li X, Davidson LA, Allred C, Patil B, Jayaprakasha G, Orr AA, Mao L, Chapkin RS, et al. (2018) Structure-dependent modulation of aryl hydrocarbon receptor-mediated activities by flavonoids. *Toxicol Sci* **164**:205–217.

Jux B, Kadow S, Luecke S, Rannug A, Krutmann J, and Esser C (2011) The aryl hydrocarbon receptor mediates UVB radiation-induced skin tanning. *J Invest Dermatol* **131**:203–210.

Kallimanis P, Chinou I, Panagiotopoulou A, Soshilov AA, He G, Denison MS, and Magiatis P (2022) *Rosmarinus officinalis* L. Leaf Extracts and Their Metabolites Inhibit the Aryl Hydrocarbon Receptor (AhR) Activation In Vitro and in Human Keratinocytes: Potential Impact on Inflammatory Skin Diseases and Skin Cancer. *Molecules* **27**:2499.

Kampa M and Castanas E (2008) Human health effects of air pollution. *Environ Pollut* **151**:362–367.

Kim JH, Kim M, Kim JM, Lee MK, Seo SJ, and Park KY (2019a) Afzelin suppresses proinflammatory responses in particulate matter-exposed human keratinocytes. *Int J Mol Med* **43**:2516–2522.

Kim KE, Cho D, and Park HJ (2016) Air pollution and skin diseases: Adverse effects of airborne particulate matter on various skin diseases. *Life Sci* **152**:126–134.

Kim M, Son D, Shin S, Park D, Byun S, and Jung E (2019b) Protective effects of Camellia japonica flower extract against urban air pollutants. *BMC Complement Altern Med* **19**:30.

Kim SH, Henry EC, Kim DK, Kim YH, Shin KJ, Han MS, Lee TG, Kang JK, Gasiewicz TA, Ryu SH, et al. (2006) Novel compound 2-methyl-2H-pyrazole-3-carboxylic acid (2-methyl-4-o-tolylazo-phenyl)-amide (CH-223191) prevents 2,3,7,8-TCDD-induced toxicity by antagonizing the aryl hydrocarbon receptor. *Mol Pharmacol* **69**:1871–1878.

Krämer HJ, Podobinska M, Bartsch A, Battmann A, Thoma W, Bernd A, Kummer W, Irlinger B, Steglich W, and Mayser P (2005) Malassezin, a novel agonist of the aryl hydrocarbon receptor from the yeast Malassezia furfur, induces apoptosis in primary human melanocytes. *ChemBioChem* **6**:860–865.

Krutmann J, Bouloc A, Sore G, Bernard BA, and Passeron T (2017a) The skin aging exposome. *J Dermatol Sci* **85**:152–161.

Krutmann J, Liu W, Li L, Pan X, Crawford M, Sore G, and Seite S (2014) Pollution and skin: from epidemiological and mechanistic studies to clinical implications. *J Dermatol Sci* **76**:163–168.

Krutmann J, Moyal D, Liu W, Kandahari S, Lee GS, Nopadon N, Xiang LF, and Seité S (2017b) Pollution and acne: is there a link? *Clin Cosmet Investig Dermatol* **10**:199–204.

Krutmann J, Schikowski T, Morita A, and Berneburg M (2021) Environmentally-Induced (Extrinsic) Skin Aging: Exposomal Factors and Underlying Mechanisms. *J Invest Dermatol* **141** (4S):1096–1103.

Lee CW, Lin ZC, Hu SCS, Chiang YC, Hsu LF, Lin YC, Lee IT, Tsai MH, and Fang JY (2016a) Urban particulate matter down-regulates filaggrin via COX2 expression/PGE2 production leading to skin barrier dysfunction. *Sci Rep* **6**:27995.

Lee CW, Lin ZC, Hsu LF, Fang JY, Chiang YC, Tsai MH, Lee MH, Li SY, Hu SC, Lee IT, et al. (2016b) Eupafolin ameliorates COX-2 expression and PGE2 production in particulate pollutants-exposed human keratinocytes through ROS/MAPKs pathways. *J Ethnopharmacol* **189**:300–309.

Lin YK, Chang CJ, Chang YC, Wong WR, Chang SC, and Pang JHS (2008) Clinical assessment of patients with recalcitrant psoriasis in a randomized, observer-blind, vehicle-controlled trial using indigo naturalis. *Arch Dermatol* **144**:1457–1464.

Liu W, Pan X, Vierkötter A, Guo Q, Wang X, Wang Q, Seité S, Moyal D, Schikowski T, and Krutmann J (2018) A Time-Series Study of the Effect of Air Pollution on Outpatient Visits for Acne Vulgaris in Beijing. *Skin Pharmacol Physiol* **31**:107–113.

Liu Y, Wei Y, Zhang S, Yan X, Zhu H, Xu L, Zhao B, Xie HQ, and Yan B (2020) Regulation of Aryl Hydrocarbon Receptor Signaling Pathway and Dioxin Toxicity by Novel Agonists and Antagonists. *Chem Res Toxicol* **33**:614–624.

Luecke S, Backlund M, Jux B, Esser C, Krutmann J, and Rannug A (2010) The aryl hydrocarbon receptor (AHR), a novel regulator of human melanogenesis. *Pigment Cell Melanoma Res* **23**:828–833.

Magiatis P, Pappas P, Gaitanis G, Mexia N, Melliou E, Galanou M, Vlachos C, Stathopoulou K, Skaltsounis AL, Marselos M, et al. (2013) Malassezia yeasts produce a collection of exceptionally potent activators of the Ah (dioxin) receptor detected in diseased human skin. *J Invest Dermatol* **133**:2023–2030.

Mancebo SE and Wang SQ (2015) Recognizing the impact of ambient air pollution on skin health. *J Eur Acad Dermatol Venereol* **29**:2326–2332.

Mataix M, Rodríguez-Luna A, Gutiérrez-Pérez M, Milani M, Gandarillas A, Espada J, and Pérez-Davó A (2020) Deschampsia antarctica extract (Edafence®) as a powerful skin protection tool against the aging exposome. *Plast Aesthetic Res.* **7**:69.

Mexia N, Gaitanis G, Velegraki A, Soshilov A, Denison MS, and Magiatis P (2015) Pityriazepin and other potent AhR ligands isolated from Malassezia furfur yeast. *Arch Biochem Biophys* **571**:16–20.

Murray IA, Krishnegowda G, DiNatale BC, Flaveny C, Chiaro C, Lin JM, Sharma AK, Amin S, and Perdew GH (2010) Development of a selective modulator of aryl hydrocarbon (Ah) receptor activity that exhibits anti-inflammatory properties. *Chem Res Toxicol* **23**:955–966.

Nakai R, Fukuda S, Kawase M, Yamashita Y, and Ashida H (2018) Curcumin and its derivatives inhibit 2,3,7,8-tetrachloro-dibenzo-p-dioxin-induced expression of drug metabolizing enzymes through aryl hydrocarbon receptor-mediated pathway. *Biosci Biotechnol Biochem* **82**:616–628.

Nakamura M, Morita A, Seité S, Haarmann-Stemmann T, Grether-Beck S, and Krutmann J (2015) Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. *Exp Dermatol* **24**:407–411.

Napolitano M and Patruno C (2018) Aryl hydrocarbon receptor (AhR) a possible target for the treatment of skin disease. *Med Hypotheses* **116**:96–100.

Nebert DW (2017) Aryl hydrocarbon receptor (AHR): "pioneer member" of the basic-helix/loop/helix per-Arnt-sim (bHLH/PAS) family of "sensors" of foreign and endogenous signals. *Prog Lipid Res* **67**:38–57.

Nobile V, Schiano I, Peral A, Giardina S, Spartà E, and Caturla N (2021) Antioxidant and reduced skin-ageing effects of a polyphenol-enriched dietary supplement in response to air pollution: a randomized, double-blind, placebo-controlled study. *Food Nutr Res* **65**:1–19.

O'Donnell EF, Saili KS, Koch DC, Kopparapu PR, Farrer D, Bisson WH, Mathew LK, Sengupta S, Kerkvliet NI, Tanguay RL, et al. (2010) The anti-inflammatory drug leflunomide is an agonist of the aryl hydrocarbon receptor. *PLoS One* **5**:e13128.

Palermo CM, Hernando JIM, Dertinger SD, Kende AS, and Gasiewicz TA (2003) Identification of potential aryl hydrocarbon receptor antagonists in green tea. *Chem Res Toxicol* **16**:865–872.

Park SL, Justiniano R, Williams JD, Cabello CM, Qiao S, and Wondrak GT (2015) The tryptophan-derived endogenous aryl hydrocarbon receptor ligand 6-formylindolo[3,2-b]carbazole is a nanomolar UVA photosensitizer in epidermal keratinocytes. *J Invest Dermatol* **135**:1649–1658.

Passeron T, Krutmann J, Andersen ML, Katta R, and Zouboulis CC (2020) Clinical and biological impact of the exposome on the skin. *J Eur Acad Dermatol Venereol* **34** (Suppl 4):4–25.

Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, and Kraus JE (2019) A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol* **80**:89–98.e3.

Polak-Witka K, Rudnicka L, Blume-Peytavi U, and Vogt A (2020) The role of the microbiome in scalp hair follicle biology and disease. *Exp Dermatol* **29**:286–294.

Rademacher F, Simanski M, Hesse B, Dombrowsky G, Vent N, Gläser R, and Harder J (2019) Staphylococcus epidermidis Activates Aryl Hydrocarbon Receptor Signaling in Human Keratinocytes: Implications for Cutaneous Defense. *J Innate Immun* **11**:125–135.

Ramadass P, Meerarani P, Toborek M, Robertson LW, and Hennig B (2003) Dietary flavonoids modulate PCB-induced oxidative stress, CYP1A1 induction, and AhR-DNA binding activity in vascular endothelial cells. *Toxicol Sci* **76**:212–219.

Rannug A (2010) The tryptophan photoproduct 6-formylindolo[3,2-b]carbazole helps genes jump. *Proc Natl Acad Sci USA* **107**:18239–18240.

Ratz-Łyko A and Arct J (2019) Resveratrol as an active ingredient for cosmetic and dermatological applications: a review. *J Cosmet Laser Ther* **21**:84–90.

Revel A, Raanani H, Younglai E, Xu J, Han R, Savouret JF, and Casper RF (2001) Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects sperm from DNA damage and apoptosis caused by benzo(a)pyrene. *Reprod Toxicol* **15**:479–486.

Revel A, Raanani H, Younglai E, Xu J, Rogers I, Han R, Savouret JF, and Casper RF (2003) Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects lung from DNA damage and apoptosis caused by benzo[a]pyrene. *J Appl Toxicol* **23**:255–261.

Richard F, Creusot T, Catoire S, Egles C, and Ficheux H (2019) Mechanisms of pollutant-induced toxicity in skin and detoxification: Anti-pollution strategies and perspectives for cosmetic products. *Ann Pharm Fr* **77**:446–459.

Robbins K, Bissonnette R, Maeda-Chubachi T, Ye L, Peppers J, Gallagher K, and Kraus JE (2019) Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis. *J Am Acad Dermatol* **80**:714–721.

Rothhammer V and Quintana FJ (2019) The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol* **19**:184–197.

Safe S, Cheng Y, and Jin UH (2017) The aryl hydrocarbon receptor (AhR) as a drug target for cancer chemotherapy. *Curr Opin Toxicol* **2**:24–29.

Schalka S, Silva MS, Lopes LF, de Freitas LM, and Baptista MS (2022) The skin redoxome. *J Eur Acad Dermatol Venereol* **36**:181–195.

Schulte KW, Green E, Wilz A, Platten M, and Daumke O (2017) Structural Basis for Aryl Hydrocarbon Receptor- Article Structural Basis for Aryl Hydrocarbon. *Struct Des* **25**:1025–1033.e3.

Seok JK, Lee JW, Kim YM, and Boo YC (2018) Punicalagin and (-)-Epigallocatechin-3-Gallate Rescue Cell Viability and Attenuate Inflammatory Responses of Human Epidermal Keratinocytes Exposed to Airborne Particulate Matter PM10. *Skin Pharmacol Physiol* **31**:134–143.

Shin JW, Lee HS, Na JI, Huh CH, Park KC, and Choi HR (2020) Resveratrol inhibits particulate matter-induced inflammatory responses in human keratinocytes. *Int J Mol Sci* **21**:1–11.

Smith KJ, Murray IA, Tanos R, Tellew J, Boitano AE, Bisson WH, Kolluri SK, Cooke MP, and Perdew GH (2011) Identification of a high-affinity ligand that exhibits complete aryl hydrocarbon receptor antagonism. *J Pharmacol Exp Ther* **338**:318–327.

Smith SH, Jayawickreme C, Rickard DJ, Nicodeme E, Bui T, Simmons C, Coquery CM, Neil J, Pryor WM, Mayhew D, et al. (2017) Tapinarof Is a Natural AhR Agonist that Resolves Skin Inflammation in Mice and Humans. *J Invest Dermatol* **137**:2110–2119.

Soshilov AA and Denison MS (2014) Ligand promiscuity of aryl hydrocarbon receptor agonists and antagonists revealed by site-directed mutagenesis. *Mol Cell Biol* **34**:1707–1719.

Szelest M, Walczak K, and Plech T (2021) A new insight into the potential role of tryptophan-derived ahr ligands in skin physiological and pathological processes. *Int J Mol Sci* **22**:1–31.

Tigges J, Haarmann-Stemmann T, Vogel CFA, Grindel A, Hübenthal U, Brenden H, Grether-Beck S, Vielhaber G, Johncock W, Krutmann J, et al. (2014) The new aryl hydrocarbon receptor antagonist E/Z-2-benzylidene-5,6-dimethoxy-3,3-dimethylindan-1-one protects against UVB-induced signal transduction. *J Invest Dermatol* **134**:556–559.

Tsai MJ, Hsu YL, Wang TN, Wu LY, Lien CT, Hung CH, Kuo PL, and Huang MS (2014) Aryl hydrocarbon receptor (AhR) agonists increase airway epithelial matrix metalloproteinase activity. *J Mol Med (Berl)* **92**:615–628.

Tsuji G, Takahara M, Uchi H, Takeuchi S, Mitoma C, Moroi Y, and Furue M (2011) An environmental contaminant, benzo(a)pyrene, induces oxidative stress-mediated interleukin-8 production in human keratinocytes via the aryl hydrocarbon receptor signaling pathway. *J Dermatol Sci* **62**:42–49.

Vijaya Chandra SH, Srinivas R, Dawson Jr TL, and Common JE (2021) Cutaneous *Malassezia*: Commensal, Pathogen, or Protector? *Front Cell Infect Microbiol* **10**:614446.

Vogeley C, Esser C, Tüting T, Krutmann J, and Haarmann-Stemmann T (2019) Role of the aryl hydrocarbon receptor in environmentally induced skin aging and skin carcinogenesis. *Int J Mol Sci* **20**:6005.

Wang L, Lee W, Cui YR, Ahn G, and Jeon YJ (2019) Protective effect of green tea catechin against urban fine dust particle-induced skin aging by regulation of NF-κB, AP-1, and MAPKs signaling pathways. *Environ Pollut* **252** (Pt B):1318–1324.

Xue Z, Li D, Yu W, Zhang Q, Hou X, He Y, and Kou X (2017) Mechanisms and therapeutic prospects of polyphenols as modulators of the aryl hydrocarbon receptor. *Food Funct* **8**:1414–1437.

Yang T, Feng YL, Chen L, Vaziri ND, and Zhao YY (2019) Dietary natural flavonoids treating cancer by targeting aryl hydrocarbon receptor. *Crit Rev Toxicol* **49**:445–460.

Yu J, Luo Y, Zhu Z, Zhou Y, Sun L, Gao J, Sun J, Wang G, Yao X, and Li W (2019) A tryptophan metabolite of the skin microbiota attenuates inflammation in patients with atopic dermatitis through the aryl hydrocarbon receptor. *J Allergy Clin Immunol* **143**:2108–2119.e12

Zamarrón A, Morel E, Lucena SR, Mataix M, Pérez-Davó A, Parrado C, and González S (2019) Extract of deschampsia antarctica (EDA) prevents dermal cell damage induced by uv radiation and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Int J Mol Sci* **20**:1–18.

Zhao H, Wu J, Wang N, Grether-Beck S, Krutmann J, and Wei L (2021) Oral Pycnogenol® Intake Benefits the Skin in Urban Chinese Outdoor Workers: A Randomized, Placebo-Controlled, Double-Blind, and Crossover Intervention Study. *Skin Pharmacol Physiol* **34**:135–145.

Address correspondence to: Carlos Rangel Rodrigues, Avenida Carlos Chagas Filho, 373. Bloco K - Sala 050, Centro de ciências da Saúde. Cidade Universitária, Rio de Janeiro, Brazil 21941-902. E-mail: rangelfarmacia@gmail.com; or Bianca Aloise Maneira Corrêa Santos, Avenida Carlos Chagas Filho, 373. Centro de Ciências da Saúde. Cidade Universitária, Rio de Janeiro, Brazil 219141-902. E-mail: bialoise.santos@gmail.com