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TITLE PAGE

Aryl hydrocarbon receptor as a therapeutical target of environmentally induced skin conditions

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RUNNING TITLE PAGE

AhR modulation in environmentally induced skin conditions

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LIST OF NONSTANDARD ABBREVIATIONS

AD - Atopic dermatitis
AhR - Aryl hydrocarbon receptor
AP-1 - Activator protein 1
ARNT - Aryl hydrocarbon receptor nuclear translocator

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BaP - Benzo[a]pyrene

BDDI - E/Z-2-Benzylidene-5,6-Dimethoxy-3,3-Dimethylindan-1-one

bHLH - Basic helix–loop–helix

BPDE - 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene

CH223191 - 2-methyl-2H-pyrazolo-3-carboxylic acid(2-methyl-4-o-tolylazo-phenyl)-amide

COX-2 – Cyclooxygenase 2

c-Src - Proto-oncogene tyrosine-protein kinase c-Src

CYP1A1 – Cytochrome P450 1A1

CYP450 – Cytochrome P450

DCT - Dopachrome tautomerase

DEJ - Dermal epidermal junction

ECM - Extracellular matrix elements

EGC - Epigallocatechin

EGCG - Epigallocatechin gallate

EGFR - Epidermal growth factor receptor

FICZ - 6-formylindole [3,2-b] carbazole

GNF351 - N-(2-(1H-indol-3-yl)ethyl)-9-isopropyl-2-(5-methyl pyridin-3-yl)-9H-purin-6-amine

HaCaT - Human keratinocyte cells

HSP90 - 90-kDa heat shock protein

IL - Interleukin

IL-1α - Interleukin-1 alpha

IL-1β - Interleukin-1 beta

IAId - indole-3-aldehyde

LBD - Ligand-binding domain

MAPK - Mitogen-activated protein kinase

MDA - Malondialdehyde

MMP - Matrix metalloproteinases

NF-κB - Nuclear factor kappa B

NHEK - Normal human epidermal keratinocytes

Nrf2 - Nuclear factor erythroid 2-related factor 2

P23 - P23 co-chaperone

PAHs - Polycyclic aromatic hydrocarbons

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PAS - Per-Arnt-Sim

PCBs - Polychlorinated biphenyls

PGE-2 - Prostaglandin E2

POPs - Persistent organic pollutants

ROS - Reactive oxygen species

SGA 360 - 1-allyl-7-trifluoromethyl-1H-indazol-3-yl]-4-methoxy phenol

TAD - Transactivation domain

TCDD - 2,3,7,8-tetrachlorodibenzo-p-dioxin

TEWL -Transepidermal water loss

TNF-α - Tumor necrosis factor-α

TSLP - thymic stromal lymphopoietin

TYRP-2 - Tyrosinase-related protein-2

UVA - Ultraviolet A

UVB - Ultraviolet B

UVR - Ultraviolet radiation

XREs - Xenobiotic responsive element

XAP2 - X-associated protein 2

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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. Here in, an overview of potential AhR ligands and their biological 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.

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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.

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1. 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 as “skin exposome” the total environmental exposures an individual undergoes throughout life that can induce or modify skin conditions (Krutmann, Bouloc, *et al.*, 2017; Passeron *et al.*, 2020). Among the exposome factors are organic air pollution, ultraviolet radiation (UVR), and the skin microbiome (through its metabolites) (Furue and Takahara, 2014; Vogeley *et al.*, 2019).

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; Caturla Cernuda N, Peral Clement A, 2019; M Kim *et al.*, 2019; 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 physiological and pathological processes, the toxic mechanism of exposome factors through the AhR pathway, and finally, discusses the use of

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synthetic compounds and natural extracts that potentially modulate AhR activation as therapeutical alternatives for skin disorders induced by environmental factors.

2. 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 (CYPs) 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, two Per-Arnt-Sim (PAS) subdomains. The PAS-A is involved in Aryl hydrocarbon receptor nuclear translocator (ARNT) dimerization and cytosolic complex interaction, while PAS-B is the ligand-binding domain (LBD) (Haarmann-Stemmann *et al.*, 2012). It also has a transactivation domain (TAD), 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 to maintain the three-dimensional structure of the receptor, protecting it from degradation, 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 non-genomic 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,

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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.*, 2012).

Among cellular responses resulting from the XREs activation, there is an increase in the expression of cytochrome P450 (CYP450) 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 (PAHs). 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 kappa 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 non-canonical pathway (Bock, 2019).

The AhR activation leads to a non-genomic response, triggering an inflammatory cascade initiated by the rapid cytosolic Ca^{2+} increase, 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 figure 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, triggering distinct responses. After an antagonist

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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 physiological 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 physiological 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 physiological and pathological 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).

3. ROLE OF AHR IN SKIN PHYSIOLOGICAL AND PATHOLOGICAL 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 lead to other harmful effects (Esser and Rannug, 2015; Schalka *et al.*, 2022).

All skin cell types express the AhR and, therefore, may response 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

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inflammatory responses, which can negatively affect the skin, resulting in pigmentation disorders; skin aging due to the degradation of Extracellular Matrix elements (ECM); 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 from ligands interaction makes it an interesting therapeutical target that is being increasingly investigated (Haarmann-stemmann *et al.*, 2015; Napolitano and Patruno, 2018).

4. EXTERNAL FACTORS THAT ACTIVATE THE AHR PATHWAY

4.1 Organic air polutants

According to the World Health Organization (WHO), about 92% of the world's population lives in cities with air pollution levels above adequate health limits (WHO, 2018).

Air pollutants can be classified into particulate matter (PM) and gases. Particulate matter can be divided according to the particle diameter into coarse particles PM10 (between 10 and 2.5μm), fine particles PM2.5 (between 2.5 and 0.1μm), and ultrafine particles PM 0.1 (<0.1μm), which is mostly composed by 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 (PAHs), such as benzo[a]pyrene (BaP), and persistent organic pollutants (POPs). The most studied POPs are dioxins, benzofurans, and polychlorinated biphenyls (PCBs), also called dioxin-like (Mancebo and Wang, 2015).

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All these pollutants 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, Moyal, *et al.*, 2017; Dréno *et al.*, 2018; Liu *et al.*, 2018), pigmentation disorders (Nakamura *et al.*, 2015; Hüls *et al.*, 2016; Grether-Beck *et al.*, 2018), skin aging (Krutmann, Bouloc, *et al.*, 2017; 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 epidemiological 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 epidemiological 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

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can lead to the generation of reactive oxygen species (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, 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 nuclear factor kappa B (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 (PM10) 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 (CW 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

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pruritus), has been shown as an AhR target gene. Epidermal levels of CYP1A1 and artemin were significantly higher in atopic patients compared to healthy patients (Furue, 2020). Therefore, pollutants may exacerbate AD symptoms by direct activation of AhR (Hidaka *et al.*, 2017; Furue, 2020).

4.2 Ultraviolet 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 leading 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-

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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).

4.3 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.* 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

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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 and Takahara, 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 patient's 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

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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 to 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, melanogenesis by TCDD and melanocyte apoptosis by malassezin, exacerbating or treating psoriasis, 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.

5. 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), immunological (Rothhammer and

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Quintana, 2019; Hui and Dai, 2020) and even cancer progression (Safe *et al.*, 2016; 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, thus acting as antagonists. Currently, the most well-accepted mechanism is that by competing with agonists for receptor interaction, 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 physiological effects are maintained and toxic effects suppressed (Esser and Rannug, 2015).

5.1 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 culture and in the skin of volunteers, shown 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 1h, but

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ineffective before 24h. It also showed effectiveness when applied after UVB-irradiation, confirming its action as AhR modulation, not as a UVR filter. In addition, the co-exposure 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 “anti-photopollution” 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” non-selective 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

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to understand the molecular interaction of active compounds with AhR in order to characterize them as safe and effective AhR modulators to the skin.

5.2 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.

5.2.1 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

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that topical treatment with eupafolin inhibits pollutant-induced COX-2 expression (C Lee *et al.*, 2016). 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 (JH Kim *et al.*, 2019).

Green tea (*Camellia sinensis*) is another rich source of polyphenols, which has been commercially used. Among its major components are epigallocatechin (EGC) 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 anti-pollution active compound for topical use, and although it was not directly demonstrated by these studies, its mechanism of action may involve AhR modulation.

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5.2.2 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 to 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).

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Tapinarof has also 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 then are quercetin (Ramadass *et al.*, 2003), harmalin and harmalol (Gendy *et al.*, 2012), Ginsenosides (Hu *et al.*, 2013), curcumin and derivatives (Nakai *et al.*, 2018) and others.

5.2.3 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 (M Kim *et al.*, 2019). 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 AhR modulation. Among the main effects of Pycnogenol® supplementation are the

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prevention of UV damage, regulation of skin pigmentation, and improvement of ECM 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 outdoors workers, highly exposed to particulate matter. It prevents transepidermal water loss (TEWL) 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 Labs, Madrid, Spain) was investigated on keratinocytes and fibroblasts exposed to UVA, UVB, and TCDD. The extract attenuated UV-induced DNA damage and pro-apoptotic 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 TEWL, 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 Zero-pollution® (Monteloeder S.L, Alicante, Spain) is a blend of 4 natural extracts which 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 (CATURLA

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CERNUDA and PERAL CLEMENT, 2019). The supplement extracts are polyphenol-rich, with a minimum content of some compounds: *Rosmarinus officinalis* leaf extract standardized at 4.5% carnosic acid + 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 (Caturla Cernuda N, Peral Clement A, 2019). 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, Rosmarinus 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).

6. 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

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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 to toxicant agonists. It is worth highlighting the differences in this study since the investigated compound was not exposed together to environmental xenobiotics, 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 biological context. If the aim is blocking a XRE-mediated toxic response such as the induction of inflammatory cytokines, both an antagonist and a 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

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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 possible repositioning 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.

AUTHORSHIP CONTRIBUTIONS

Participated in research design: Accioli, Santos and Rodrigues.

Performed data analysis: Accioli and Santos.

Wrote or contributed to the writing of the manuscript: Accioli, Silva, Santos and Rodrigues.

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FOOTNOTES

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FIGURE CAPTION LIST

Figure 1. Functional structure of Aryl hydrocarbon receptor (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.

Figure 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, 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,

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among other responses. (DXN, dioxin; PAH, polycyclic aromatic hydrocarbon; MLZ, malassezin; FICZ, 6-formylindole [3,2-b] carbazole; COX-2, cyclooxygenase-2; CYP1A1, cytochrome p450 1A1 enzyme; AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; XRE, xenobiotic responsive elements; HSP90, 90-kDa heat shock protein; P23, P23 co-chaperone; XAP2, X-associated protein 2; ROS, reactive oxygen species).

Figure 3. Summary of external factors that activate the AhR pathway and the potential consequences of this activation in the skin. Organic air pollutants, ultraviolet 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, inflammatory conditions aggravation, such as acne, atopic dermatitis, psoriasis, and sensibility, as well as skin carcinogenesis process.

TABLES

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

Compound	Experimental model	Biological Result	Ref

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synthetic compound	E/Z-2-Benzylidene-5,6-Dimethoxy-3,3-Dimethylindan-1-One (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 co-exposure 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, MAPK and NK-κB activation; *In vivo* inhibition of COX-2 expression in PM-treated mice.	(LEE et al., 2016 a)
	Afzelin	keratinocytes (HaCaT);	Inhibition of PM-induced intracellular ROS, p38 MAPK, AP-1 activation and IL-1α expression.	(KIM et al., 2019 a).
	epigalocatequina-galato (EGCG)	Primary human epidermal keratinocytes	Inhibition of PM-induced intracellular ROS, and TNF-α, IL-1β, IL-6, IL-8 e MMP-1expression.	(SEOK et al., 2018)
		human dermal fibroblasts	Increase of cell viability and reduction of PM-induced MMPs expression, and	(WANG et

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	(HDF)	NF-κB and MAPKs activation.	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 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)

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Natural extracts	*Camellia japonica flower extract*	keratinocytes (NHDF) Human skin explants (*ex vivo*)	Inhibition of pollutant-induced XREs activity and CYP1A1 expression and reduction of intracellular ROS and MMP-1 expression in NHDFs; Reduction of pyknotic nuclei cells and MDA leves, prevention of DEJ detachment, and improvement of ECM density in urban pollutant-exposed skin explants.	(KIM et al., 2019 b)
	Deschampsia 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)
	Deschampsia 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)
	R. officinalis, O.Europaea, L. citriodora and *S.japonica* leaf extracts	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.	(CATURLA CERNUDA;

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(Zero-pollution®)			PERALCLEMENT.,2019)
	Clinical study (Oral supplementation)	Improvement of elasticity, firmness, 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 *Pinus pinaster*)	Clinical study (Oral supplementation)	Prevention of skin dehydration, TEWL, skin darkening and improvement of viscoelastic properties in outdoor workers under high air pollution conditions	(ZHAO et al., 2021)
Rosmarinus 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)

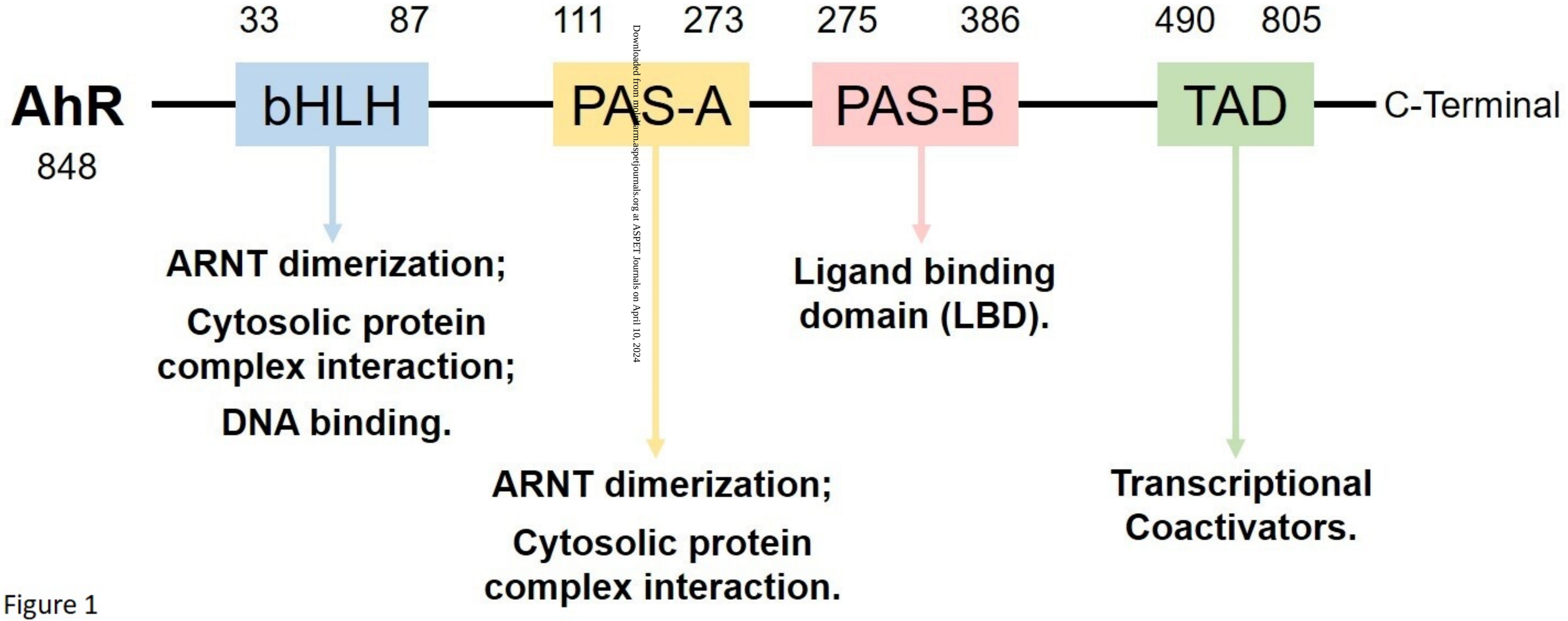

Figure 1

Figure 2

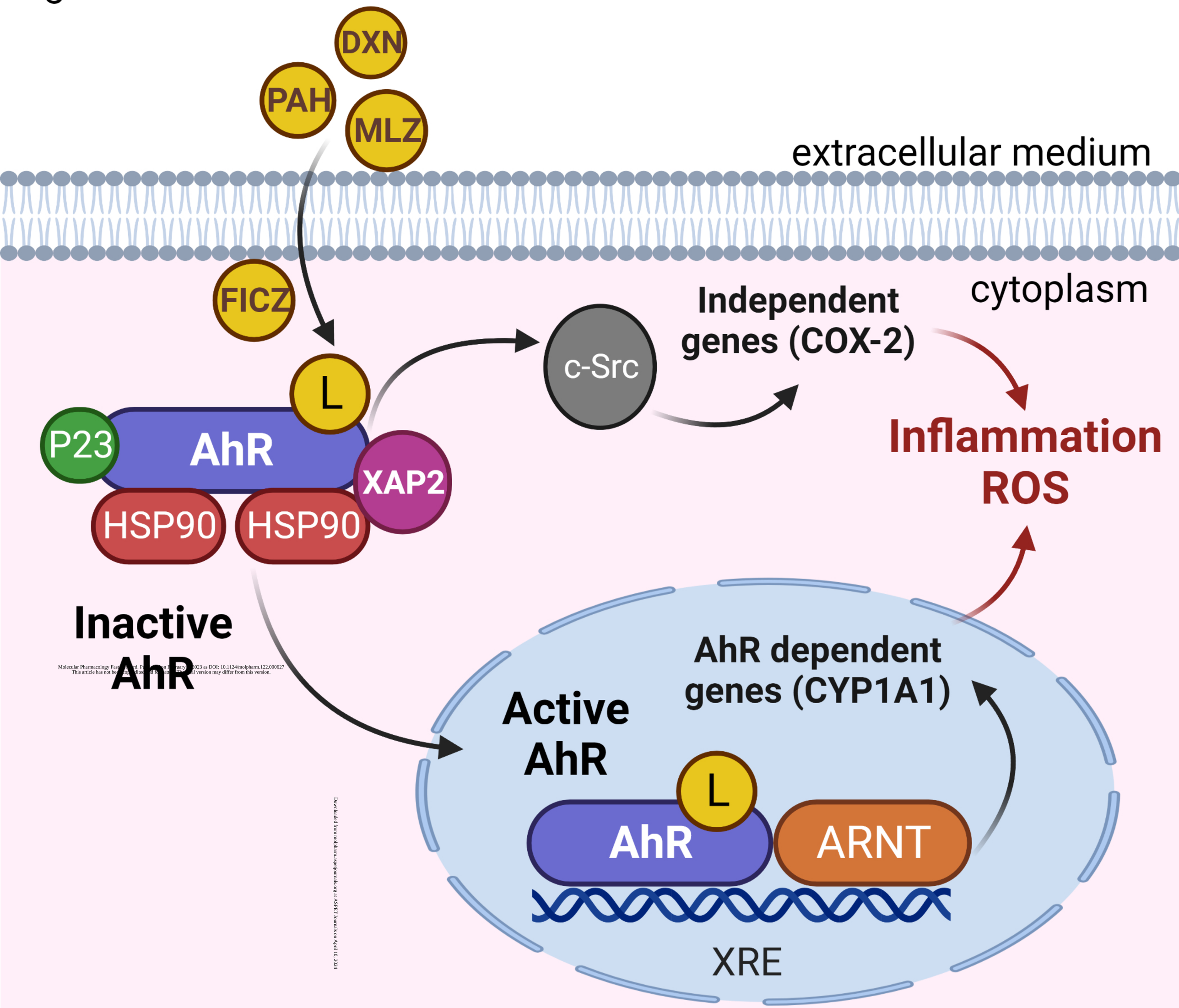

Figure 3