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FROM COMEDONES TO WRINKLES: MOLECULAR MECHANISMS OF POLLUTION-INDUCED SKIN DAMAGE AND CLINICALLY-PROVEN THERAPEUTIC STRATEGIES

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Abstract

This skin damage that is a result of pollution is one of the most universal but least considered dermatological health in the contemporary times and the World Health Organization reports that nine in ten people breathe air with pollutant levels high. The presented extensive review follows the molecular continuum of early acneiform lesions to deep wrinkles development after exposure to cutaneous pollutants, and a single mechanistic pathway is formed, based on the aryl hydrocarbon receptor (AhR)-reactive oxygen species (ROS)-inflammation axis. Conserved signaling cascades, such as canonical (CYP1 induction) and non-canonical (c-Src/EGFR), converge upon oxidative stress, matrix metalloproteinase activation, and impaired extracellular matrix synthesis, depending on the airborne presence of particulate matter, polycyclic aromatic hydrocarbons and gaseous pollutants. Importantly, we find a critical lack of literature, namely the lack of a temporospatial model of the relationship between acute pollutant-induced comedogenesis and chronic extracellular matrix degradation. We solve this problem by suggesting the concept of oxinflammatory memory, which is based on temporary pollution exposures that cause irreversible cellular changes in terms of epigenetic changes, mitochondrial dysfunction, and cell senescence. The review concludes with a critical analysis of the clinically-validated interventions, such as the widely-researched CF Mix antioxidant preparation (15% vitamin C, 1% vitamin E, 0.5% ferulic acid) which has shown protection of pollutant-induced barrier disruption and collagen degradation in controlled human studies, and new AhR-modulating agents and laser combination approaches. The combination of the mechanistic knowledge and evidence-based therapeutic approach makes this review offer a roadmap to dermatologists and researchers concerning the prevention and reversal of the cutaneous pathology caused by pollution at the clinical spectrum.

1. INTRODUCTION: THE POLLUTION DERMATOLOGY PARADIGM

1.1 The Scale of Environmental Threat to Skin Health

The interface of the human skin with the environment has been changed radically during the contemporary period. With the rapid intensification of global urbanization in a never-before-seen speed of urban growth, the cutaneous surface, the largest organ of the human body and the main barrier of exposure to a complex of anthropogenic pollutants is the frontline. The World Health Organization estimated in 2018 that 9 out of 10 individuals breath polluted air

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with a high level of pollutants in it, with ambient (outdoor) air pollution being responsible of 4.2 million premature deaths per year in the world(Bocheva, Slominski, & Slominski, 2023). Such shocking figure is not only a respiratory and cardiovascular problem but a widespread dermatological issue that has only recently started to be given the necessary scientific scrutiny. This physical barrier (the skin, about 1.8 square meters in an average adult) and an interface with metabolic activity must deal with particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), gaseous pollutants, heavy metals and volatile organic compounds. The skin is constantly exposed, and relatively unprotected unlike the lungs, which have the advantage of a mucociliary clearance mechanism, or the gastrointestinal tract, which has a large system of detoxification(Sieradocha, 2024). The implications of this unremitting environmental attack are somewhat dramatic: population-based research has established beyond reasonable doubt that chronic exposure to airborne PM, especially combustion generated PM2.5, hastens cutaneous aging and reduces the quality of life of individuals exposed to it. These effects have been measured in recent real-life experience with startling precision. A research study that was groundbreaking and was presented in the European Academy of Dermatology and Venereology (EADV) 2025 Congress involved 150 women in China, comparing the experiences of those with sensitive skin in modern urban contexts to similar women living in less urbanized and traditional contexts. The results showed that individuals living in the city and having sensitive skin had almost triple or more amounts of prostaglandin E2 (PGE2) which is one of the main markers of inflammation than people living in the country. Additionally, oxidative stress indicators were also found to be 16 percent greater in delicate skin when it came to metropolitan environments, whereas noticeable indicators of harm such as augmented pores, uneven shade and age spots were also substantially more abundant . Such data can convert the abstract pollution statistics to real biological effects and show that the exposome of contemporary life leaves quantifiable molecular traces. There is a significant economic and quality-of-life aspect of the skin damage caused by pollution. Sensitive skin in isolation affects a population of up to 70 percent of the entire world and this specific condition is increasing by 68 percent in the last 20 years, the same way the world is becoming urbanized in the world. In addition to the clinical presentation, premature aging, chronic inflammation, and visible pigmentary alterations disrupt self-confidence and present a high cost to healthcare. Since life expectancy is increasing and the modern world population over 60 years of age is expected to pass two billion by 2050, the health effects of environment-accelerated cutaneous aging is an urgent concern of the people(Denisow-Pietrzyk, 2021).

1.2 From Acne to Aging: A Clinical Continuum

The relationship between environmental pollutants and skin disease is not a novel observation. Historical accounts of occupational dermatoses among chimney sweeps and industrial workers documented what we now recognize as pollution-induced cutaneous pathology, though the mechanistic underpinnings remained elusive. Chloracne, the severe acneiform eruption resulting from exposure to halogenated aromatic compounds, provided an early model for understanding how environmental chemicals could selectively target the pilosebaceous unit . These historical observations established that pollutants do not merely irritate the skin superficially but engage specific biological pathways with distinct clinical consequences.

What has emerged from contemporary research is the recognition that these clinical manifestations exist along a continuum—from the acute, follicular pathology of comedogenesis to the chronic, degenerative changes of extracellular matrix degradation culminating in wrinkle formation. This "comedone-to-wrinkle trajectory" serves as an organizing principle for understanding pollution dermatology as an integrated field rather than a collection of disparate observations. The same molecular mechanisms—aryl hydrocarbon receptor (AhR) activation, oxidative stress generation, and inflammatory cascade initiation—operate across this clinical spectrum, though their temporal

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dynamics and cellular targets vary(Khunger & Dash, 2025) .

At the comedone end of this continuum, pollutants—particularly PAHs deposited on the skin surface—penetrate the follicular infundibulum, where they alter sebum composition through squalene peroxidation, induce follicular hyperkeratinization, and trigger perifollicular inflammation . These events mirror and amplify the pathogenic processes underlying acne vulgaris, explaining the epidemiological links between urban residence and acne severity. Moving along the continuum, repeated pollutant exposures generate cumulative oxidative stress that targets melanocytes, leading to the irregular hyperpigmentation and lentigines documented in Asian and European cohort studies . Finally, at the wrinkle end of the trajectory, sustained matrix metalloproteinase (MMP) activation and impaired procollagen synthesis progressively degrade the dermal architecture, producing the coarse wrinkles and loss of elasticity characteristic of pollution-aged skin.

This conceptual framework carries profound implications for clinical practice: early intervention at the comedone stage may prevent progression to irreversible matrix degradation. The recognition that pollution-induced damage operates as a continuum rather than discrete pathologies transforms prevention from a cosmetic consideration to a therapeutic imperative(Santamaria, Gilaberte, Prudkin, & Piquero-Casals, 2025).

1.3 Scope and Objectives of This Review

The connection between the environment pollutants and the skin disease is not a new finding. The historical descriptions of occupational dermatoses in chimney sweeps and industrial workers were the forerunners of what we now understand as pollution-induced cutaneous pathology, but the underlying mechanistic basis was never understood. A major breakthrough in the study of how environmental chemicals may be selective against the pilosebaceous unit came with chloracne, the acute form of acne caused by exposure to halogenated aromatic compounds. These historic observations put in place that the pollutants are not only skin-deep irritants but they invoke certain biological pathways with definite clinical implications. What has come out of the modern research is the understanding that these clinical manifestations lie on a spectrum- the acute, follicular pathology of comedogenesis to the chronic, degenerative, alterations of extracellular matrix degradation to the formation of wrinkles. This comedone-to-wrinkle sequencing is a principle of organization that is used to cognize pollution dermatology as a unified field and not a series of unrelated observations(Marrot & Nouveau, 2022). The identical molecular pathways, i.e., the aryl hydrocarbon receptor (AhR) activation, the production of oxidative stress, the initiation of inflammatory cascades work within the same clinical spectrum, but their time dynamics and their targeting cells differ . At the comedone end of this spectrum, pollutants, especially PAHs on the surface of the skin, diffuse into the follicular infundibulum, where they modify the composition of sebum by squalene peroxidation, cause follicular hyperkeratinization, and cause perifollicular inflammation . The pathogenic processes underlying acnes vulgaris are reflected and increased in these events, which justify the epidemiological associations between urban residents and the severity of acne. Going down the continuum, repeated exposures to pollutants cause cumulative oxidative stress, which acts on melanocytes resulting in the irregular hyperpigmentation and lentigines reported in Asian and European cohort studies(Marrot & Nouveau, 2022) . Last, the prolonged activation of matrix metalloproteinase (MMP) and failure to produce procollagen in the end of the wrinkle trajectory gradually deteriorates the dermal architecture resulting in the coarse wrinkles and elasticity loss of pollution-aged skin. The conceptual framework has very deep implications regarding clinical practice: early intervention when the stage of comedone is detected can prevent the advancement to the stage of irretrievable matrix degradation. The understanding that the harm caused by pollution is not discrete pathologies but a continuum is something that changes the idea of

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prevention into a cosmetic one and makes it a treatment necessity(Han, Seok, & Park, 2025).

1.4 The "Oxinflammatory Memory" Concept: A Novel Framework

The main gap in the scientific knowledge that has been filled by this review is the temporal-spatial gap in the literature between the acute and chronic pollution effects. The contemporary studies have emerged in two parallel, although mostly unrelated lines. Acute exposure studies (hours-days) have beautifully clarified immediate molecular reactions on one track; AhR nuclear translocation, activation of cytochrome P450, generation of oxidative bursts, cytokine discharge, short-term changes in barricade proteins(Han et al., 2025). Epidemiologic cohort studies of years to decades have been carried out on the parallel track showing strong relationships between accumulating pollution exposure and clinical outcomes: wrinkles severities, lentigines, and validated skin aging indices. The missing component, which is critical, is a mechanistic framework, which describes the transformation of acute and reversible changes into permanent and progressive tissue damage. To bridge this gap we suggest the concept of the oxinflammatory memory. This model assumes that temporary exposure to pollution causes long-term cellular changes in at least four dynamic processes. To start with, epigenetic alterations are an interesting hypothesis of mediation of pollutant memory. The current developments in cutaneous epigenetics have clarified that environmental exposures regulate the structure of DNA methylation, histone modifications, and chromatin architecture, imposing lasting alterations on the expression of genes that persist beyond the original insult(Martic, Jansen-Dürr, & Cavinato, 2022). Exposure to pollution (especially by the formation of oxidative stress), can cause global hypomethylation as well as localized hypermethylation at certain regulatory elements. A similar study showed that exposure to PM2.5 triggers ten-eleven translocation (TET) enzyme but inhibits DNA methyltransferases, which causes the demethylation of p16INK4A promoter, and causes cellular senescence thereof . These epigenetic scars can be accumulable over time, gradually changing the cutaneous cells to pro-inflammatory, pro-senescent phenotypes. Second, sustained pro-oxidative conditions may be created by metabolic reprogramming of cutaneous cells after exposure to pollutants(Martic et al., 2022). Chronic production of low levels of reactive oxygen species to mitochondrial dysfunction (such as in the form of accumulated mitochondrial DNA mutations and blocked electron transport chain activity) can cause a lasting oxidative stress even after the stimulating exposure is removed. Such a metabolic memory can be the reason to explain the constant tendency toward high oxidative stress levels among urban populations despite temporary changes in pollution. Third, the inflammatory loop feedback mechanism may sustain tissue inflammation by the presence of sustained transcription factor signaling and autocrine cytokine signaling in the absence of persistent pollutant exposure. The oxinflammation theory, where oxidative stress and mild inflammation feed off of each other in a vicious cycle, gives the understanding of how acute insults may trigger self-sustaining tissue damage . Fourth, cellular senescence and the senescence-associated secretory phenotype (SASP) is another form of terminal expression of pollutant memory. The aging effect of pollution may be partially due to accumulation of p16 / p21-positive senescent cells, secreting pro-inflammatory cytokines, matrix metalloproteinases and growth factors that break down tissue architecture and hamper regeneration and repair and is progressive and irreversible in nature. The oxinflammatory memory model has testable predictions and provides novel therapy options. Should transient exposures induce permanent cellular changes, intervention timing becomes essential then not only do you need to prevent the acute effects, but also the formation of molecular memory. Besides, this framework indicates that acute protection through surrogate endpoints might not be a reliable predictor of long-term benefits and that anti-pollution claims need testing against chronic outcomes. Through the incorporation of this new notion, we can no longer consider the destruction of the skin caused by pollution as a final, unchangeable effect of

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living in modern society but a biological process that can be changed, and where we can find potential solutions to prevent and intervene on an individual level(Ferrara, Prieux, Woodby, & Valacchi, 2021).

2. The Exposome of Skin Aging: Characterizing Pollutants and Their Cutaneous Interactions

2.1 Classification of Cutaneous Pollutants

The environment of the atmosphere to which the human skin is exposed has a complicated combination of various pollutants having different physicochemical properties that define their interactions with the skin. This classification can be used to understand the greatest dermatological risk of pollutants and to create specific protection measures. Particulate matter (PM) is a category of cutaneous pollutants that has been examined most widely, and is broken into three major fractions based on aerodynamic diameter(Ferrara et al., 2021; Haykal et al., 2025). Coarse (PM10) particles are those which have a dust, ash, pollen, and smoke particulates that formed during mechanical actions and combustion and have an aerodynamic diameter that is less than 10 micrometers in diameter. The fine particles (PM2.5) of less than 2.5 micrometers in diameter usually occur as a result of burning wood or fossil fuels, such as car emissions and industry operations. The smallest particle fraction (PM0.1), less than 0.1 micrometers, is largely comprising of the combustion sources, and with the highest surface area-to-mass ratio, such particles have higher biological reactivity. The PM composition varies significantly depending on a source but generally contains elemental carbon, sulfates, nitrates, ammonium, metals and adsorbed organic compounds such as polycyclic aromatic hydrocarbons . Another significant group of cutaneous toxicants is gaseous pollutants. Ozone (O3), which is a highly reactive oxidant, is the product of photochemical reactions of nitrogen oxides and volatile organic compounds; which poses a specific danger to the skin barrier functions. Combinations of fossil fuel burning and industrial processes are responsible for the production of nitrogen dioxide (NO2) and sulfur dioxide (SO2). Studies of occupational exposure situations have confirmed that the ability to penetrate the skin is limited at occupational concentrations of oxides of nitrogen and sulfur that are up to lethal levels in the air (e.g. 3000 ppm) although they still can have a surface effect via direct oxidative reaction with stratum corneum lipids and proteins(Haykal et al., 2025). Much attention should be paid to polycyclic aromatic hydrocarbons (PAHs) as the class of critical ligands that activates the aryl hydrocarbon receptor (AhR) pathway. These lipophilic substances are formed during partial burning of organic matter and are found in high concentrations in diesel emissions, cigarette smoke and industrial emissions, in barbecue smokes and other sources of cooking. Increased molecular-weight PAHs are more likely to be attached on particles, with fine particles (smaller than 1.8 mm across) playing the leading role in the transport of high molecular-weight PAHs. Such property of having particles that bind is relevant to dermal exposure because PAHs depositing on the skin surface can then be subsequently penetrated or released out of their particle carriers over lengthy durations. The presence of heavy metals in contaminated air, such as nickel, cobalt, iron, copper, and vanadium, is the cause of cutaneous toxicity; this is mainly due to their redox property. These metals are involved in Fenton chemistry, which produces reactive oxygen species, which trigger oxidative stress cascades. Nanocatalyst derivatives of nickel and cobalt oxides have been reported to cause dose- and time-dependent loss of cell viability, oxidative stress, and transcriptional factor AP-1 and NF-kB activation of epidermal cells . Notably, when metal nanoparticles are co-exposed to ultraviolet B radiation, these effects are enhanced, implying synergies between classes of pollutants and solar radiation(Hergesell, Valentová, Velebný, Vávrová, & Dolečková, 2022).

Volatile organic compounds (VOCs) such as toluene, xylene, styrene, and benzene are a group of air lipophilic pollutants that pose a very high dermal absorption risk. Non reactive VOCs like toluene, m-xylene and styrene show higher and quicker rates of dermal absorption than polar VOCs like acetone and tetrahydrofuran and penetration of polar compounds is mostly

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restricted to the surface and stratum corneum of the skin. The estimates of human exposure in relation to non-reactive VOCs indicate that the dermal exposure contributes between 2 to 18 percent of the inhalation route to the total body burden, which implies that the transdermal uptake makes a significant contribution to the overall body burden under consideration(Damevska, Simeonovski, Darlenski, & Damevska, 2021).

2.2 Skin Penetration: Routes and Kinetics

The two main routes through which the pollutants penetrate the skin are the transepidermal and the transfollicular route through hair follicle openings and continuous stratum corneum, respectively. All the pathways have their peculiarities, which determine the kinetics and the degree of ingress of pollutants. The predominant pathway of the majority of pollutants is the transepidermal absorption which implies diffusion through stratum corneum that is the surface layer of the epidermis. The penetrating molecule is controlled by the physicochemical characteristics of the penetrating molecule, especially lipophilicity, molecular weight and ionization state. The stratum corneum can be described as a heterogeneous barrier which is constituted of protein-enriched corneocytes embedded in a lipid matrix that is arranged in multilamellar bilayers(Savita, 2025). Initial studies by Rothman determined that there is a surface-located obstacle at the junction of cornified and non-cornified epidermis which is situated in the stratum lucidum area, which also possesses specific selective properties of permeability. Later studies by Szakall separated this barrier membrane and found it to be a thin, flexible, structure with high concentrations of sulfhydryl groups that is insoluble to fat solvents, which suggested it was proteinaceous. The polarity of most pollutants, especially the PAHs and non-reactive VOCs, enables them to partition into the and across the intercellular lipid matrix(Savita, 2025). On the one hand, higher molecular-weight PAHs are more affine to particles, and it can actually increase dermal exposure because particles that are retained form a reservoir effect in which pollutants are released gradually as and through particles that are retained on the skin surface. Transfollicular pathways offer another path which avoids the undamaged stratum corneum. The ratio of hair follicles to total skin area is about 0.1 to 1 percent, however they may absorb a disproportionate amount of pollutants in the form of particulate pollutants. Nanoparticles such as PM0.1 are capable of penetrating through hair follicles and reaching the perifollicular dermis, and possibly to antigen presenting cells, such as Langerhans cells, and regional lymph nodes. This follicular pathway is specifically relevant to pollutant-bound particles, since the infundibular epithelium does not have the stratum corneum of the interfollicular epidermis that is fully differentiated, so the level of barrier is less. The integrity of skin barriers is an important variable in determining pollutant ingress. The stratum corneum is the first line of defence, and those disorders that impair its integrity, such as genetic deficiencies of filaggrin, inflammatory skin diseases, including atopic dermatitis and psoriasis, mechanical damage, or chemical damage, increase the penetration of pollutants. Pan et al. showed that urban PM can enter the skin more easily when the barrier is disrupted and results in reactive oxygen species-dependent cutaneous inflammatory reactions in vivo. The two-way interaction in which pollutants cause and worsen dysfunction of barriers and this vicious cycle increases cutaneous damage. The dynamics of dermal absorption is one of the most crucial factors of the particle size. The coarse particles (PM10) become mainly localized on the skin surface or in the stratum corneum layers that are near the skin, which can be washed or desquamated. Fine particles (PM2.5) have greater penetration capacity of getting into openings of the follicles and could possibly get to the viable epidermis. The potency of penetration of ultrafine particles (PM0.1) is the most intense, and clinical studies have shown that they can penetrate the dermis and even the systematic circulation(Araviiskaia et al., 2019) . A study of the exposure to barbecue fume indicated that particle quantities deposited on the forearm are correlated with the intake of coarse particles at the dry deposition flux but insignificantly connected with

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fine particles, which may indicate that the particle size can influence not only the deposition but the subsequent absorption performance as well. There has been a development in the experimental models of conducting studies on cutaneous uptake of pollutants. In lieu of the gold standard of percutaneous absorption assessment, ex vivo human skin in Franz diffusion cells has remained the gold standard. Nonetheless, it is not easy to get samples of human skin, and this has resulted in the extensive use of animal models. Rat skin, especially dorsal sections of animals of age (at least seven weeks old) exhibit consistent stratum corneum densities and can orchestrate fairly accurately on human absorption of a hydrophilic liquid molecule e.g. N-methyl-2-pyrrolidone and N,N-dimethylformamide . But with solid lipophilic compounds such as most pollutants, rat skin can be two- to three-fold more likely to take up the compound than human skin, and care should be taken to make extrapolations. More advanced designs feature micropig Franz cell membranes that are similar to human skin tissue and have been used to test the dermal intake of airborne VOCs in controlled conditions . In vitro human epidermis models EpiDerm FT EpiDerm FT is a standardized and reproducible system used experimentally to determine the toxicity of pollutants and has been used to evaluate the tissue injury, oxidative stress and accumulation of inflammatory mediators induced by metal nanoparticles. These cell culture models allow mechanistic research and minimize the use of animal testing and limitations on availability of human tissues(Mistry, 2017).

[TABLE 1: Classification and Cutaneous Effects of Major Environmental Pollutants]

Pollutant Class	Key Examples	Primary Sources	Skin Penetration	Molecular Targets	Clinical Associations
Particulate Matter (PM2.5)	Combustion-derived particles, diesel exhaust	Traffic, industry, wildfires	Follicular, disrupted barrier	AhR, mitochondria, cell membrane	Premature wrinkles, pigmentation, inflammation
Polycyclic Aromatic Hydrocarbons	Benzo[a]pyrene, naphthalene, anthracene	Fossil fuel combustion, tobacco	Transdermal (lipophilic)	AhR, CYP enzymes, DNA	Comedones, lentigines, skin aging
Gaseous Pollutants	Ozone (O_3), NO_2, SO_2	Photochemical reactions, industry	Diffuse across stratum corneum	Lipids, antioxidants, proteins	Barrier disruption, oxidation
Heavy Metals	Iron, copper, nickel, vanadium	Industrial emissions, brake dust	Ion channel-mediated	Fenton chemistry, enzymes	Oxidative stress, inflammation
Volatile Organic Compounds	Benzene, toluene, formaldehyde	Solvents, paints, furnishings	Transdermal	Cellular proteins, DNA	Irritant reactions

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3. Molecular Mechanisms: The Unified Pathway from Surface to Senescence

3.1 The Aryl Hydrocarbon Receptor: Master Regulator of Pollutant Response

At the summit of the cutaneous response to environmental pollutants is the aryl hydrocarbon receptor (AhR), which is a ligand-activated transcription factor mobilizing a multi-faceted network of xenobiotic metabolism, oxidative stress production, inflammatory pathways, and finally tissue remodelling and aging. It is important to understand the structure, function and signaling pathways of AhR in order to gain insight into the ways in which diverse pollutants: polycyclic aromatic hydrocarbons and dioxin-like compounds converge on a single mechanism of skin damage(Tran, 2024).

AhR cutaneous biology structure and function. The human AhR is a protein of 848 amino acids consisting of a number of functional domains that are important in its function as an environmental sensor. These contain a basic helix-loop-helix (bHLH) DNA-binding domain and two Per-Arnt-Sim (PAS) subdomains: PAS-A and PAS-B, which are necessary in heterodimerization with the AhR nuclear translocator (ARNT) and form the ligand-binding pocket. AhR is ubiquitously expressed in all of the key cell types of the skin, such as keratinocytes, fibroblasts, melanocytes, Langerhans cells, and other populations of immune cells in the skin . Such a wide pattern of expression is indicative of the basic functions of the receptor in ensuring cutaneous homeostasis and meeting environmental demands. AhR occurs in cytoplasm in the rest posture and is part of a multiprotein complex consisting of a dimer of the heat-shock protein 90 (HSP90), AhR-interacting protein (AIP), co-chaperone p23, and soluble tyrosine kinase c-Src. Such geometry keeps AhR in the state of conformationally competent ligand binding but inhibits transcriptional activity and pre-premature nuclear translocation. Activation of ligands: xenobiotic agonist PAHs. The importance of AhR in causing skin damage by pollutants lies in the fact that this substance is activated by certain groups of pollutants, especially, polycyclic aromatic hydrocarbons (PAHs). PAHs are ubiquitous environmental pollutant that is formed in the process of incomplete combustion of organic substances, and the key sources of PAH are vehicle emissions, industrial production, cigarette smoke, barbecue smoke, and domestic heating process. Such lipophilic compounds are deposited on the surface of the particulate matter (especially the fine (PM2.5) and the ultrafine (PM0.1) particles and contribute to their deposition on and further penetration into the skin. When PAHs are released off their particle carriers into cells, they diffuse through cell membranes, and reach the cytoplasm, directly interacting with the PAS-B domain of AhR. The interaction of this ligand and its receptor triggers conformational changes, which lead to the dissociation of the multiprotein complex, revealing nuclear localization signals, which causes the signaling cascade. Canonical signaling: CYP induction and nuclear translocation. Due to the ligand-induced nuclear translocation of the receptor, the canonical AhR signaling pathway commences. After the dissociation of AhR with its cytoplasmic chaperones, the protein is released into the nucleus where it heterodimerizes with ARNT, its binding partner. The AhR-ARNT complex then identifies and binds with particular DNA sequences referred to as xenobiotic response elements (XREs), or dioxin response elements (DREs) in the promoter of target genes. Transcriptional targets of AhR are prototypical and encode phase I xenobiotic-metabolizing enzymes, which include CYP1A1, CYP1A2, and CYP1B1 cytochrome P450 members. These monooxygenases are the enzyme that catalyzes the first step in the metabolism of PAH and adds one atom of molecular oxygen into the substrate and the other atom to water. Although this reaction elevates the polarity of PAHs and enables their conjugation and excretion, it produces a large amount of highly reactive intermediates, such as epoxides and quinones, which can produce DNA adducts and engage in redox cycling to form reactive oxygen species (ROS) . Various reports indicate that CYP mRNA and protein expression are increased by PM exposure in vitro and in vivo, making this a reliable biomarker of AhR activation after exposure to pollutants. Non-canonical pathways c-Src release and EGFR transactivation.

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Along with its genomic signaling by nuclear translocation, AhR activation activates non-canonical pathways which play a major role in pollutant-induced cutaneous injury. When the ligand is bound and dissociated with the cytoplasmic multiprotein complex the released and activated tyrosine kinase c-Src is then released and activated . The released c-Src then phosphorylates and activates the epidermal growth factor receptor (EGFR) and triggers the downstream signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway. This non-genomic signaling results in transcriptional upregulation of XRE-independent genes including those of aldo-keto reductase (AKR) 1 isoforms, which could be involved in oxidative stress and inflammatory reactions(Tran, 2024). The c-Src/ EGF is one of the significant amplification pathways in which AhR stimulation can cause faster modulation of the cellular behavior without the need to involve the slower nuclear translocation, gene expression, and production of proteins. Cell type-specific AhR reactions. The cell-specific patterns of gene expression and physiological functions are reflected in the functional consequences of AhR activation that differ significantly across different cell types of the skin. AhR activation has a role in the differentiation, barrier, and inflammatory functions of keratinocytes, the most common cell type in the epidermis, in keratinocytes. Activation of AhR in keratinocytes by ligands increases the expression of CYP1A1/1B1, causes oxidative stress, and increases the expression of pro-inflammatory cytokines such as interleukin (IL)-1a, IL-6, and IL-8 . Moreover, AhR signaling of keratinocytes may change the expression of differentiation markers including filaggrin and loricrin which may weaken the barrier integrity . AhR stimulation in fibroblasts, the major mesenchymal cells of the dermis, induces the expression of matrix metalloproteinases (MMPs) and in particular MMP-1 (collagenase-1) and MMP-9 (gelatinase) which catalyze the breakdown of extracellular matrix components such as collagen and elastin. This is a fibroblast-specific reaction which is the direct cause of the dermal aging and wrinkles that are a direct result of pollution-aged skin. Activation of AhR in melanocytes enhances melanogenesis by transcriptionally activating the rate limiting melanin-synthetic enzyme, tyrosinase, and by increasing the expression of melanogenic paracrine factors by adjacent keratinocytes . This is the reason why the exposure to pollution has been clinically associated with the lentigines and irregular hyperpigmentation. AhR regulates the inflammatory polarization of immune cells, such as Langerhans cells and infiltrating lymphocytes, having effects on the pro-inflammatory versus regulatory polarization of these immune cells. The cell type-selectivity of AhR responses highlights the multifacetedness of the pollution-induced skin pathology and the necessity to take into account all of the skin compartments when designing therapies(Österlund et al., 2023).

3.2 Oxidative Stress: The Common Currency of Pollution Damage

Oxidative stress is the key mechanistic point where various pollutants have their harmful influence on the skin structure and functioning. Oxidative stress is defined as a disproportion between the generation of reactive oxygen species (ROS) and the ability of antioxidant defense systems to counteract it, damaging lipids, proteins, and DNA and in the process stimulating inflammatory and aging-related signal transduction pathways. Pollutant chemical property generation of ROS directly. Pollutants have the ability of producing ROS in several ways that are not directly related to the metabolism of a cell. Redox-active compounds present on the surface of the particles of particulate matter, especially those of combustion origin, include transition metals, such as iron, copper, nickel, and vanadium. The metals are involved in Fenton as well as the Haber-Weiss chemistry where hydrogen peroxide is reduced to hydroxyl radical which is very reactive (OH). Moreover, the PAHs bound on the surface of the particles may be activated under the influence of photochemical activation in the presence of the solar energy, causing the formation of singlet oxygen (1O2) and other ROS as a result of the type II photodynamic reaction . The findings of Ibuki and others showed that when human skin

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fibroblasts were exposed to combinations of both BaP and ultraviolet A (UVA) radiation, the exposure resulted in serious cytotoxicity in the cells which was the production of an oxidative DNA damage, 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG). Notably, this destruction was inhibited by singlet oxygen quenchers and not by hydroxyl radical or superoxide anion scavengers, which suggests that photodynamic production of singlet oxygen is a key pathway of PAH-based phototoxicity . These results demonstrate that the chemical properties of pollutants together with other exposome factors result in the production of ROS via non-enzymatic reactions which directly attack the cellular constituents. Dysfunction of the mitochondrion and the electron transport chain. The mitochondria are targets as well as sources of oxidative stress caused by pollutants(Misra et al., 2021). Exposure to PM impairs mitochondrial functioning via several pathways, such as direct induction of electron transport chain complexes, dissipation of the mitochondrial membrane potential and mitochondrial permeability transition induction . The effects of these perturbations include leakage of electrons of complexes I and III in which escaped electrons react with molecular oxygen to form superoxide anion (O2*-). Oxidative damage is especially susceptible to mitochondrial DNA (mtDNA), which does not have the protection of the histone packing and effective repair mechanisms that nuclear DNA possesses. This process causes mitochondrial dysfunction and an increase in ROS generation by accumulated mtDNA mutations that damage the synthesis of subunits of the electron transport chain coded in the mitochondrial genome in a vicious cycle. This mitochondrial aspect of oxidative stress caused by pollutants could also play a role in the suggestion of an oxinflammatory memory concept in this review since the damage to the mitochondrial DNA may continue and extend the oxidative signal even after the harmful agent that causes the oxidative stress has stopped. AhR /p47phox pathway stimulation of NADPH oxidase. Along with direct ROS production and dysfunction of mitochondria, pollutants stimulate specialized enzymatic systems of ROS formation, in particular, the NADPH oxidase (NOX) family. Research has also shown that the PM exposure triggers ROS generation by the AhR/p47phox/NOX2 pathway(Zieneldien et al., 2025) . Transcriptional upregulation of NOX subunits accentuates on AhR activation and nuclear translocation, whereas non-genomic systems could also play a role in NOX activation. One of the main organizers of NOX2 complex formation is the p47phox subunit which is stimulated after exposure to pollutants and allows catalytic subunits to translocate to the membrane where superoxide anion is produced . This signaling cascade forms an amplification loop wherein AhR activation caused by pollutant-produced PAHs causes oxidative stress both via CYP-mediated metabolism and NOX-mediated production of superoxide. Meeting of these pathways with AhR further confirms its role as the overall controller of pollutant-mediated cutaneous oxidative injury. Unfolded protein response and endoplasmic reticulum stress. Another organelle that is susceptible to the oxidative stress destined by the pollutants and adds to the total ROS burden of the cell is the endoplasmic reticulum (ER). The exposure of PM alters the homeostasis of ER, causing misfolded or unfolded proteins build up and triggers the unfolded protein response (UPR) . The UPR and ER stress have a close relationship with oxidative stress in a variety of ways: protein misfolding in the ER can use glutathione and generate ROS during the formation of disulfide bonds; the UPR can induce the expression of ER oxidoreductin 1 (ERO1), which forms hydrogen peroxide during oxidative protein folding; and long-term ER stress may result in mitochondrial ROS generation via calcium-dependent mechanisms. Another complicated aspect of the oxidative stress phenotype is the integration of ER stress pathways into the pollutant response network and it also creates more therapeutic targets that can be manipulated. Exhaustion of the natural antioxidant systems. The skin has a complex system of antioxidant defenses that is aimed at countering ROS and preserving redox homeostasis. These are enzymatic antioxidants,

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which include superoxide dismutase (SOD), catalase, and glutathione peroxidase, and non-enzymatic small molecules such as glutathione, vitamin C (ascorbic acid), and vitamin E(a -tocopherol) . The sustained or excessive exposure to pollutants overloads these defense mechanisms, and the antioxidant stores is lost and the cellular balance changes to a pro-oxidative one. Urban population studies have shown that there is a lower antioxidant capacity and an increase in oxidative stress markers than in rural populations, and that environmental pollution exerts a long-lasting stress on cutaneous antioxidant defense. Their loss of glutathione, the most prevalent intracellular thiol antioxidant, is of great importance because it not only invalidates direct scavenging of ROS but also glutathione S-transferase (GST)-mediated detoxification of electrophilic pollutants as well as their metabolites(Pambianchi, 2021) . This decline in antioxidant potential creates a lax space in which oxidative injury spreads throughout the cellular compartments and within the macromolecular targets.

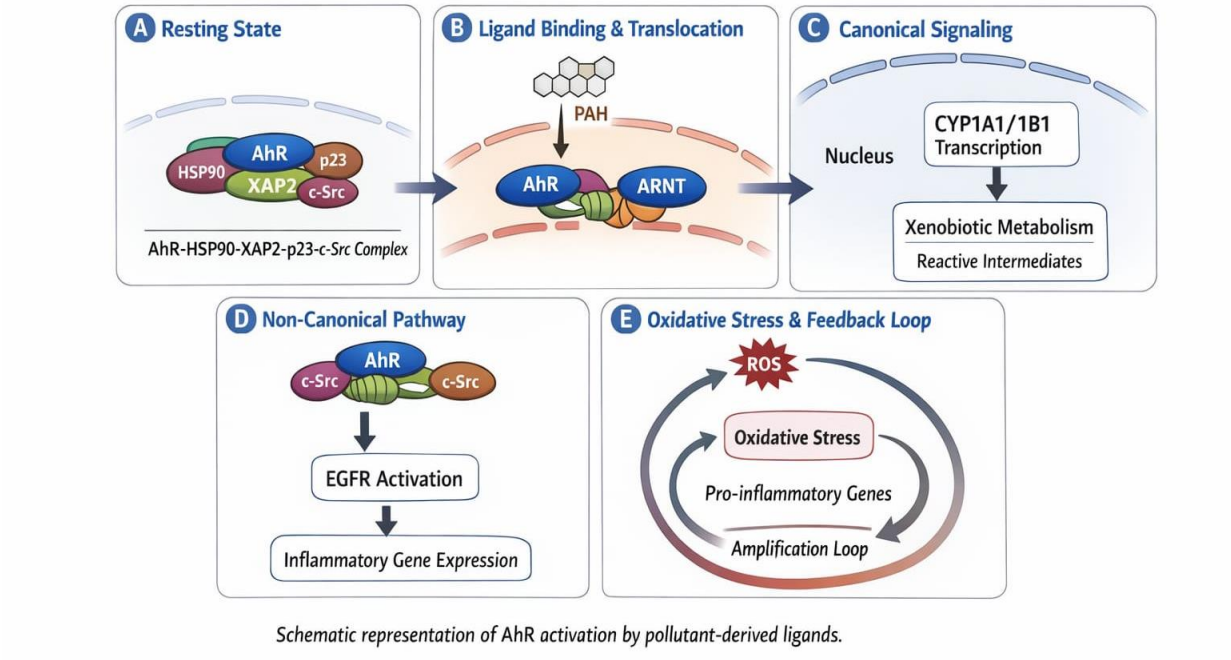


Figure 1: [The Aryl Hydrocarbon Receptor Signaling Cascade in Cutaneous Cells]

Schematic representation of AhR activation by pollutant-derived ligands. (A) In the resting state, AhR resides in the cytoplasm complexed with chaperone proteins (HSP90, XAP2, p23) and c-Src. (B) PAH binding induces conformational change, nuclear translocation, and heterodimerization with ARNT. (C) Canonical signaling leads to CYP1A1/1B1 transcription and xenobiotic metabolism, generating reactive intermediates. (D) Non-canonical pathways involve c-Src release, EGFR activation, and downstream inflammatory gene expression. (E) The resultant oxidative stress creates a feed-forward amplification loop.

3.3 Inflammatory Cascades and the "Oxinflammation" Concept

Oxidative stress and inflammation are closely interrelated processes that support each other in a vicious circle, a fact that is becoming more and more accepted as oxinflammation. This assumption is based on the fact that the production of pollutant-induced ROS leads to inflammatory processes leading to an increase in oxidative stress, and the cycle of tissue destruction and functional impairment begins. NF-kB and pro-inflammatory cytokine. One of the major connections between oxidative stress and inflammation is the transcription factor nuclear

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factor kappa-light-chain-enhancer of activated B cells (NF-kB). NF-kB is also bound to inhibitor of kB (IkB) proteins and kept in the cytoplasm by unstimulated cells. The activation of IkB kinases (IKKs) by ROS, especially hydrogen peroxide, leads to the phosphorylation and ubiquitination of IkB that is degraded by proteasomes. NF-kB released moves into the nucleus and binds kB response element within the enhancer regions of target genes, which results in the transcription of a wide range of pro-inflammatory mediators. They consist of cytokines (tumor necrosis factor-alpha, TNF-a), interleukins (interleukin-1 alpha, IL-1a) interleukin-1 beta, interleukin-6, IL-6; chemokines (CXCL8, IL-8); adhesion molecules (intercellular adhesion molecule 1, ICAM-1); enzymes (cyclooxygenase-2, COX-2) and inducible nitric oxide synthase (iNOS The generation of these mediators brings on board and activates immune cells, enhances the inflammatory process and produces more ROS as a result of the respiratory burst of the infiltrating neutrophils and macrophages. The stressed keratinocytes per se are able to secrete an extensive repertoire of chemokines such as CXCL1/2/3/4/8 recruiting neutrophils that release more ROS propagating further epidermal alterations(Passeron et al., 2021).

Upregulation of COX-2/PGE2 pathway. Inducible enzyme (COX-2) involved in the production of prostaglandins is also upregulated upon exposure to the pollutants via NF-kB and MAPK clearances at all times. COX-2 is responsible in converting arachidonic acid into prostaglandin H 2 which is then further mediated into prostaglandin E 2 (PGE2) by tissue-specific synthases which is a potent pro-inflammatory factor. PGE2 facilitates vasodilation, edema, and pain and also has an effect on cellular growth and survival. COX-2 and PGE2, in the light of skin injury as a result of pollution, leads to inflammatory cell infiltration, epidermal hyperplasia and activation of matrix metalloproteinases. Notably, COX-2/PGE2 pathway also plays a role in the melanogenesis, which offers a mechanistic connection between inflammation caused by pollution and hyperpigmentation. This has been clinically relevant with the recent real-life data published by the EADV 2025 Congress that showed that urban dwellers with sensitive skin showed almost three times more PGE2 levels than their counterparts in the rural areas. Inflammasome activation (NLRP1, NLRP3). The inflammasome platform is a very crucial IL-1 family cytokine activation and release platform. After exposure to the pollutants, the NLRP1 and NLRP3 inflammasomes may be stimulated in cutaneous cells. The activation of inflammasomes generally involves two signals: a priming signal which increases the expression of inflammasome components and pro-IL-1b (which can often be delivered via the activity of NF-kB), and an activation signal which promotes the assembly of the complex and the activation of caspase-1. Several damage-associated molecular patterns (DAMPs) produced upon pollutant exposure may be used as stimulations, such as extracellular ATP, uric acid crystals, mitochondrial DNA, and lysosomal destruction upon particle phagocytosis . Pro-IL-1b and pro-IL-18 are cleaved by active caspase-1 to their secreted forms releasing powerful pyrogenic and inflammatory mediators. In particular, IL-1b enhances inflammation by acting through both paracrine and autocrine feedback, which leads to its induced expression and to that of other cytokines and chemokines. T-cell polarization (Th17/Treg imbalance). In addition to innate immune activation, the exposure to pollutants affects adaptive immunity by altering the T-cell differentiation and functionality. Activation of AhR on T cells and antigen-presenting cells can shift the ratio between the pro-inflammatory (Th17) and the anti-inflammatory (Tregs) T cells. Based on the ligand setting, AhR signaling can induce Th17 differentiation (that leads to IL-17 secretion and neutrophilic inflammation) or Treg differentiation (that leads to immunosuppression and tissue regeneration). The balance has significant implications on skin pathology caused by pollution: Th17 skewing can cause aggravation of inflammatory dermatoses such as atopic dermatitis and psoriasis and impaired Treg functionality may allow uncontrolled inflammatory reactions to environmental stimuli . The vicious cycle of oxinflammation. The

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bidirectional mutual reinforcement of oxidative stress and inflammation of pollutant-exposed skin is captured in the concept of oxinflammation. NF-kB, inflammasome, and MAPK signaling Oxidative stress operates through inflammatory mediation by NF-kB, inflammatory response, and NOX enzyme induction and depletion of antioxidant defenses: The cascades of oxidative stress trigger inflammatory responses which, in turn, increase oxidative stress NLX enzyme induction and loss of antioxidant defense: Inflammatory mediators and antioxidant defenses mediate their own induction of oxidative Such a vicious cycle is how chronic inflammatory conditions and progressive tissue damage may be triggered by an acute exposure to pollutants. As the oxinflammation model emphasizes, key to reducing the intensity of a highly active inflammatory baseline is to interfere with the process at multiple stages: the anti-oxidant effect might not be sufficient to down-regulate the highly active oxidative mediators of inflammation, nor the anti-inflammatory effect of oxidative stress on other cells to block the oxidative basis of inflammation(Nobile et al., 2021).

3.4 Barrier Disruption: The Gateway to Progressive Damage

Stratum corneum is the main physical and biochemical barrier to internal milieu attack on the environment. Exposure to pollutants breaks this barrier in various ways and damages its integrity, making it an opening to further destruction. Down-regulation of filaggrin, loricrin and involucrin. The epidermal differentiation complex proteins, such as filaggrin, loricrin and involucrin, are necessary to form an intact stratum corneum. During cornification, filaggrin assembly of the keratin filaments is carried out and later broken down into natural moisturizing factors that maintain the hydration and acidity. Transglutaminases cross-link lacticrin and involucrin to create the cornified envelope, the insoluble protein framework which strengthens the corneocyte. Exposure to PM plays a major role in reducing the expression of these important barrier proteins. In reconstructed human epidermis, and models, both in vivo and in vitro, it has been shown that PM, especially PM containing PAH, suppresses the expression of filaggrin and loricrin, both on mRNA and protein levels. According to Pan and colleagues, urban PM with PAHs (SRM 1649b) blocked filaggrin expression in porcine skin, which relates to the growth of transepidermal water loss (TEWL) and the increase of topical drug permeability. Such a down regulation of differentiation proteins might be mediated partly by AhR-induced blockage of normal keratinocyte differentiation programs, and by oxidative stress-induced interference with cellular signaling. Tight junction proteins degradation (ZO-1, occludin). Under the stratum corneum, the tight junctions between the granular layer keratinocytes create a second barrier which limits the movement of water, solutes and possible pathogens through paracellsular. Among the major tight junctions, there are zona occludens-1 (ZO-1), occludin, and claudins. The tight junction integrity is impaired by PM exposure in several ways. Immunohistochemistry of Pan et al. revealed that PAH-rich PM (1649b) inhibited the expression of E-cadherin, which disrupts adherens junctions that interact with tight junctions in barrier activity . Oxidative stress was produced by PM and is able to directly alter the tight junction proteins directly through carbonylation and other oxidative damages affecting their assembly and activity. Also, PM-induced inflammatory cytokines, especially, TNF-a and IL-1b, have been reported to destabilize tight junctions via NF-kB and myosin light chain kinase (MLCK) signaling. It breaks down both stratum corneum and tight junction barriers to form a permissive effect on the increased penetration of pollutants, forming a feed-forward mechanism of continuous barrier degradation. Stratum corneum and lipid peroxidation. Ceramides, cholesterol and free fatty acids, which form intercellular lipid matrix of stratum corneum, are lamellar bilayers, which are vital to the barrier functionality. These lipids can be oxidized by ROS that are formed by pollution. The process of lipid peroxidation, which starts with the hydroxyl radical obtaining of hydrogen atoms on polyunsaturated fatty acids, produces lipid hydroperoxides, and reactive aldehydes that include malondialdehyde and 4-hydroxynonenal.

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The products which disrupt membrane integrity and fluidity, are also secondary messengers that may alter proteins and DNA. Lipid peroxidation of the stratum corneum interferes with its highly structured lamellar structure of barrier function, making it more permeable and allowing the influx of other pollutants and allergens into the skin. This process is made worse by the depletion of the body antioxidants which are found in large quantities in the stratum corneum, especially vitamin E and which ordinarily shields the membrane lipids against oxidative damage(Rolfes, Singh, Haarmann-Stemmann, & Krutmann, 2025).

Microbiome changes and dysbiosis. Microbiome The cutaneous microbiome refers to a group of diverse communities of bacteria, fungi, and viruses that are important in ensuring the optimal health of the skin by competitively excluding pathogens, synthesizing antimicrobial peptides and regulating local immune responses. There is an emerging body of evidence that pollutant exposure changes the composition and activity of the skin microbiome, which is the cause of barrier dysregulation and inflammation. Comparisons of urban and rural populations have demonstrated that there are differences in microbial diversity and relative abundance of individual taxa but the exact nature of dysbiosis caused by pollution is still an area of ongoing research. Skin microbiota can be AhR ligands, specifically Malassezia species which synthesize strong AhR-activating compounds such as malassezin and indirubin . On the other hand, alterations in the cutaneous chemical environment caused by pollutants might also prefer certain microbial populations to others and suppress others, perhaps pro-inflammatory species. Clinical effects: enhanced permeability, sensitization. The accumulation of effects of barrier disruption caused by the pollutants is augmented percutaneous permeability to environmental agents and augmentation of the danger of sensitization. City residents show very poor hydration of the skin and impaired barrier activity in comparison to rural ones, though they may have more strict skincare regimes in place. This barrier compromise helps in the permeation of not only pollutants but also other xenobiotics, allergens and irritants that would have otherwise not been permitted through. Thus, people in polluted areas exhibit higher rates and degrees of irritant and allergic contact dermatitis and sensitivity to topical products. The mutual dependence between the disruption of barricades and inflammation results in a self-perpetuating loop in which the compromise in the barrier allows increased penetration of pollutants, which leads to further inflammation and further damage of the barriers(Rolfes et al., 2025).

3.5 DNA Damage and Genotoxic Consequences

Genotoxic effects of pollutant exposure constitute the most basic approach in cell injury, and the possible outcomes may include acute cytotoxicity and mutagenesis and carcinogenesis. Adducts of DNA with metabolites of PAH. In order to cause genotoxic effects, PAHs need to be metabolically activated. After a CYP1A1 and CYP1B1 induction by AhR, PAHs like benzo[a]pyrene are changed into reactive intermediate, and it is mainly bay-region diol epoxides. The final carcinogenic metabolite of BaP is benzo[a]pyrene-7, 8 diol-9,10-epoxide (BPDE) which reacts with exocyclic amino group of guanine to form BPDE-N2-dG adducts. These cumbersome DNA adducts, unless repaired by nucleotide excision repair (NER) preceding DNA replication, may result in mutations that are mutagenic, of the same type: G-T transversions that activate oncogenes or silence tumor suppressor genes. Measures of PAH-DNA adducts in human populations have shown high levels in people with a higher exposure to pollutants, which has supported the importance of this pathway to real-life exposure situations. Oxidative base alterations (8-oxo-dG). Besides the formation of bulky adducts, the ROS formed by pollutants also cause oxidative DNA damage, the most common of which is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), which is mutagenic as it tends to mispair with adenine during replication to produce G-T transversions just like those obtained by PAH adducts. Various sources of 8-oxo-dG after exposure to pollutants include direct ROS generation by the chemical properties of pollutants, ROS generation during PAH metabolism, ROS generation by activated

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inflammatory cells and photodynamic reaction between PAHs and UVA radiation(Ferrara, 2021). In the study by Ibuki et al. the coexposure of human skin fibroblasts to BaP and UVA by the authors resulted in a substantial formation of 8-oxo-dG of human skin fibroblasts via singlet oxygen generation, which was inhibited by the antioxidant N-acetyl-L-cysteine. In a study of personal exposure to air pollutants, Sorensen et al. established that the 8-oxo-dG in lymphocyte DNA was significantly positively correlated with individual PM2.5 exposure, thus providing a direct correlation between the actual pollution in the real world and the oxidative destruction of DNA. The breakage of the strands and aberrations. ROS has the ability to directly cut off the DNA phosphodiester backbone to single-strand breaks (SSBs). In case two SSBs are within a short distance on opposing strands, or replication forks come across unrepaired SSBs, double-strand breaks (DSBs) may be produced--highly toxic lesions that when incompletely repaired lead to chromosomal aberrations, such as deletions, translocations and amplifications. Exposure to PM causes DNA strand break in cultured cells and in exposed humans. According to Sorensen and others, the DNA strand breaks in lymphocytes were found to be high in the summer period when the levels of pollution and the amount of sunlight were more implying that they interacted to produce the genotoxic effects. There have also been reports of chromosomal aberrations such as the formation of micronucleus after exposure to pollutants, which means that DNA damage has occurred to the degree that structural chromosomal aberration is noted. DNA damage response and repair. Cells detect DNA damage by means of a coordinated set of signaling networks which is known as the DNA damage response (DDR). DDSBs and replication stress activate ataxia telangiectasia mutated (ATM) and ATM -rad3 (ATR) kinases respectively and phosphorate downstream effectors such as checkpoint kinases CHK1 and CHK2. These signal cascades cause a state of cell cycle arrest that gives the cell time to repair its DNA and then continue the cell cycle of replication or mitosis. Bulky PAH-DNA adducts are mainly removed by nucleotide excision repair (NER), whereas oxidative lesions, including 8-oxo-dG, are repaired through base excision repair (BER). Repair gene expression, such as ERCC1 (NER) and OGG1 (BER), exhibits a seasonal change, which is associated with the amount of damage to DNA, and is likely to be adaptively regulated based on environmental stress. But once the damage exceeds the repair capability, or repair ability is impaired by some form of cell damage, sustained DNA damage causes apoptosis or senescence the consequences of which have profound implications on tissue homeostasis and aging. Implication on mutagenesis and skin cancer(Ferrara, 2021). The eventual effect of unrepaired or inaccurately repaired DNA damage is mutagenesis, or permanent distortions of DNA sequence that are transmitted to daughter cells. The G-T transversion signature of both PAH adducts and 8-oxo-dG are commonly seen in TP53 mutations in smoking-related skin cancer, which offers a molecular basis of carcinogenesis caused by the effect of pollutants. Although the relationship between air pollution and non-melanoma skin cancer is not as definitively determined as that of lung cancer, mechanistic evidence is in support of a contributory effect, especially when used in conjunction with UV radiation. The observation that pollutants cause the damage of DNA in various ways: the formation of adducts, oxidative modification, and photodynamic enhancement indicate the significance of the carefully designed genoprotective methods(Ko, 2021).

[TABLE 2: Key Molecular Mediators of Pollution-Induced Skin Damage]

Mediator	Upstream Activators	Downstream Effects	Cell Types	Pathological Role	Therapeutic Targetability
AhR	PAHs, TCDD,	CYP1 induction,	All skin cells	Master regulator	High (multiple antagonists in development)

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	PM-bound ligands	ROS, inflammation			
CYP1A1/1B1	AhR activation	PAH metabolism, ROS generation	Keratinocytes, fibroblasts	Genotoxicity, oxidative stress	Moderate
NF-κB	ROS, TLR activation	IL-6, IL-8, TNF-α, COX-2	Keratinocytes, immune cells	Inflammation	High (established pathway)
COX-2	NF-κB, MAPK	PGE2, MMP induction	Keratinocytes, fibroblasts	Inflammation, matrix degradation	High (NSAID class)
NLRP1/3	ROS, lysosomal damage	IL-1β, IL-18	Keratinocytes, macrophages	Pyroptosis, inflammation	Emerging
MMP-1, MMP-9	ROS, AP-1, NF-κB	Collagen degradation	Fibroblasts, keratinocytes	Wrinkle formation	Moderate
p53	DNA damage	Cell cycle arrest, apoptosis	All cells	Senescence, cancer protection	Context-dependent

4. Clinical Manifestation 1: Comedogenesis and Acneiform Eruptions

4.1 Historical Observations: The "Greasy Chin" Phenomenon

The appreciation of the fact that environmental pollutants are capable of causing acnesiform breakouts is over a century old even before modern mechanistic realization. Initial accounts of industrial worker dermatoses described typical occupational patterns of follicular pathology which we currently know to be pollution induced cutaneous injury. Of these historical observations, the greasy chin phenomenon proved to be a distinct clinical abnormality of workers who had been in contact with combustion products, tars, and industrial chemicals, and where comedones and inflammatory lesions appeared in a distribution pattern indicating contact with the environment. Chloracne as a prototype of follicular pathology caused by pollutants. The most widely studied and prototypical type of acnes-causing pollutant eruption is chloracne, recognized by Herxheimer and von Bettman almost a century ago. Exposure to halogenation aromatic hydrocarbons induces this characteristic dermatosis which includes polychlorinated dibenzo-p-dioxin (especially TCDD), polychlorinated dibenzofurans and polychlorinated biphenyls. Chloracne unlike common acne vulgaris is typified by formation of many comedones and light yellow cysts spread mostly on the malar region, behind the ears and on the genitals and may be accompanied by the arms, shoulders, buttocks and thighs. The pathologic characteristic of chloracne is hyperkeratinization of the outer root sheath and sebaceous duct epithelium resulting in the infundibular dilation and the development of keratinized cell layers and sebum in the follicular lumen(Ghalamghash, 2025) . Notably, this effect happens without the hormonal effects of acnes vulgaris such as those that generally cause the disease, making it clear that environmental chemicals have the ability to directly regulate the biology of keratinocytes to cause follicular pathology. The sebaceous glands themselves are also subject to metaplastic alterations and sebocytes are replaced by keratinizing epithelial cells, which adds to the characteristic clinical appearance. Chloracne therefore offers a priceless experimental system of how the pollutant-stimulated signaling pathways, especially the aryl hydrocarbon receptor pathway, can stimulate

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comedogenesis and inflammation of the follicles in the absence of conventional acnes stimulants.

4.2 Mechanisms of Pollution-Induced Comedogenesis

The pathogenesis of comedogenesis, triggered by pollution, is a complex chain of events that influence follicular keratinization, sebum composition, interactions with microbes, and recruiting of inflammatory cells, which all focus on the pilosebaceous unit. Changes in sebum composition: squalene peroxidation. One such critical inducing event of the comedogenesis caused by pollutants is the oxidative alteration of sebum lipids, especially squalene. A triterpene that contains about 10-12% of the human sebum, squalene is the only triterpene with six double bonds, and therefore is the most readily oxidizable constituent of lipids of the surface, in the skin. Combination of environmental pollutants such as ozone, nitrogen dioxide, and particulate matter with the ultraviolet radiations is a strong oxidizing agent and enhances squalene peroxidation. Squalene peroxidation has a biological meaning because its oxidation products are biologically active. The comedogenesis is directly caused by squalene by-products which are mostly in the form of peroxidases and also play a role in the formation of inflammatory acne. These oxidized lipids have comedogenic properties that lead to hyperkeratinization of the follicles and that are pro-inflammatory mediators that continue the acnesiform response. Moreover, the squalene peroxide has been implicated in the dark yellow discoloration that takes place in the skin under oily conditions, indicating that sebum oxidation may play a role, not only in the development of lesions, but also in the apparent appearance of the skin. The understanding that the products of squalene oxidation are valid biomarkers of atmospheric pollution on the skin has created new opportunities to measure the risk of exposure to the individual and evaluate protective measures. AhR-mediated differentiation alterations result in follicular hyperkeratinization. The aryl hydrocarbon receptor (AhR) is the key protein that connects the exposure to pollutants with the change in keratinocyte differentiation and follicular hyperkeratinization. The elegant studies on the prototypical AhR ligand TCDD have shown that AhR activation has a direct effect on the expression of human epidermal differentiation complex genes. Sutter et al. showed that AhR-activated by TCDD reacts to xenobiotic response elements (XREs) located upstream of filaggrin (FLG) gene and boosts its expression and epidermal barrier development(Juhaščik, Kováčik, & Huerta-Ángeles, 2022) . Out of 19 genes of epidermal differentiation complex analyzed, 14 were found to be upregulated with exposure to TCDD, such as filaggrin and small proline-rich protein 2. This AhR mediated increased differentiation has direct clinical implications in follicular pathology. Halogenated hydrocarbons in chloracne increase the hyperplasia of the keratinocytes of the outer root sheath and the sebaceous duct resulting in the deposition of the multi-layers of keratinized cells in the dilated follicular infundibulum. The resultant comedone is the combination of these accumulated keratinized cells mixed with sebum from which it is structurally equivalent to the comedones of acne vulgaris but is provoked by a different environmental stimulus. The hyperkeratinization response is an irreversible change in the biology of keratinocytes and not mere irritability by the fact that the response is selective to follicular epithelium and the response is dose dependent. Propionibacterium acnes contact with pollutants. A connection between pollutants exposure and the cutaneous microbiome, especially with references to Cutibacterium acnes (previously Propionibacterium acnes) is a relatively new research field. Although there is still scarce direct evidence on pollutants-induced changes in C. acnes behavior, the pro-inflammatory condition caused by oxidation of sebum and hyperkeratinization of the follicles probably affects the colonization and activity of bacteria. Squalene and lipid peroxidation products are oxidized to produce free radicals that increase the inflammation to provide the acne-causing bacteria with a favorable environment. The resulting oxidative environment can contribute to the proliferation of certain C. acnes phylotypes, or increase the pro-inflammatory capabilities of these

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types, but additional studies are required to clarify these relationships. Pilosebaceous inflammatory infiltrations. The pilot stage of the comedone formation into inflammatory acne lesions is the inflammatory process through recruitment of immune cells into the pilosebaceous unit. The oxidative stress of pollutants leads to the expression of pro-inflammatory mediators by keratinocytes and sebocytes, which form chemotactic gradients to draw in neutrophils, lymphocytes, and macrophages. Research on the environmental oxidative stress has shown that the process of lipid peroxidation produces free radicals that directly increase inflammation directly. This inflammatory element plays a vital role in the clinical manifestation of acne induced by pollution because inflamed lesions have a higher chance of scarring as well as post-inflammatory dyspigmentation compared to unaffected comedones(Peno-Mazzarino et al., 2024).

4.3 Clinical Evidence Linking Pollution to Acne

The environmental pollution and acne relationship is not limited to the historical observations of occupations but includes the present epidemiological data of the urban population of the world. Urban epidemiological researches. Researchers Yang and others have put forward four key pillars of influencing factors on the onset and progression of acne, which include individual socio-economic and biological factors, social environmental factors, built environmental factors, and natural environmental factors. Of the natural environmental factors, one can identify temperature, humidity, sun exposures, and air pollution which can be regarded as triggers that worsen the acne in patients. The understanding that environmental influences, such as urbanization, have on the presence of acnes has been complexely intertwined with the role of built environmental factors, such as green space in densely populated regions and transit systems, in affecting the quality of the air, and thus acne prevalence. Exposure to traffic and the severity of acne. Traffic-related air pollution, which is characterised by the presence of elevated concentrations of particulate matter, nitrogen dioxide, and polycyclic aromatic hydrocarbons, is a notably topical exposure to an urban population. Research involving analysis of distance to large roads has shown that it is related to inflammatory skin diseases. A study of more than 14,000 cases of childhood patients conducted by National Jewish Health found that with each tenfold increase in distance to a major roadway, the likelihood of developing atopic dermatitis had been reduced by 18.8 percent, indicating that traffic-related pollutants had a direct impact on the occurrence of inflammatory skin diseases in children. Although similar studies with a more specific focus on acne are scarce, mechanistic similarities on the effect of pollutants in causing inflammation in atopic dermatitis and acnes show that similar relationships are also plausible. Temporal studies in the periods of pollution. The use of temporal relationships between acoustic pollution events and acnes exacerbations is an added support of causal relationship. Both seasonal factors and meteorological conditions, which entrap pollutants, and sudden events like wildfires have been linked to higher dermatologic complaints. The identification of the fact that the immediate contact with air pollutants contributes to outpatient visits of inflammatory skin conditions indicates that people prone to developing acnes can have flares when the quality of air is poor. The observations correlate with the recommendations regarding increased protection of the skin in the case of the pollution episodes, especially in cases of people with the pre-existing acne or sensitive skin(Kang et al., 2025).

4.4 Implications for Acne Management in Polluted Environments

The acknowledgment that the environment pollutes and this pollution is part of the pathogenesis of acne has great implications on clinical treatment especially the patients living in or travelling to the urban areas with a high level of pollution. Antioxidant acne requirements. The pivotal contribution of oxidative stress, especially the squalene peroxidation, to the process of pollutants-induced comedogenesis is a solid argument in favor of including antioxidants into the lines of treatment of acnes. Research has

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suggested that the use of topical antioxidant may be beneficial in enhancing the follicular environment, which reduces lipid peroxidation, and, therefore, the incidence of acne may decline as a result of antioxidant application in the topical form. It is supported by clinical evidence in the form of studies of antioxidant preparations in patients with acne. In a Brazilian study of 56 participants with mild to moderate acne, a serum of 0.5 percent silymamarin (an antioxidant of milk thistle), 15 percent L-ascorbic acid and 0.5 percent ferulic acid applied once a day in 12 weeks was tested. At the end of the study, patients registered a 45 percent mean decrease in the quantity of inflammatory lesions, and a 43 percent decrease in the quantity of non-inflammatory lesions when contrasted to the baseline and a Sebumeter test showed the patient had reduced oil on the skin surface by 16 percent in just one week of use. Further research has also established that antioxidant serums can be used to supplement prescription acne treatment. In one of the studies done in the United States and Germany, prescription acne regimens with the addition of the same silymarin-containing antioxidant serum decreased facial erythema by 60, dryness by 49 and scaling by 67% on average. Such data show that antioxidant formulations will meet a new therapy requirement in acne, especially in patients with both acne and skin aging issues, by reducing the oxidative element of the damage caused by the pollution and enhancing the tolerability of traditional treatments of acne. Adjunctive therapy: Barrier protection. The association between skin barrier functioning and the exposure to pollution is significant to acne management. Pollutants affect barrier integrity in several ways such as lipid peroxidation, disrupting tight junctions, and down-regulation of differentiation proteins. Such a compromise of barriers allows greater intrusion of contaminants and irritants, forming a vicious circle of non-stop destruction. Antioxidant formulation trials in clinical conditions have shown to protect against barrier perturbation by pollutants with both barrier proteins such as involucrin and loricrin preserved after PM and UV exposure. The addition of barrier protecting agents to acne treatment can therefore have two-fold benefits; it can decrease the infiltration of pollutants and also decrease the irritability of traditional acnes drugs. Pollutant avoidance mechanisms. In patients with acne where there is polluting environment, avoidance techniques are a significant supplement to pharmacologic treatment. Interventions can be suggested based on restricting the time of outdoor activities in response to the most active pollution periods, physical protection with the help of protective clothing, and complete, but mild cleansing to eliminate the traces of the pollutants without disrupting the barriers. Another avenue that patients can adopt by reducing their exposure to cutaneous pollutants is the development of film-forming polymers and other physical barriers of the pollutant as a constituent of skincare formulations. Since the literature is still actively working to explain the mechanisms through which pollution leads to acne, evidence-based patient education and lifestyle modification recommendations will be increasingly perfected(El Haddad, Gerbaka, Hallit, & Tabet, 2021).

5. Clinical Manifestation 2: Pigmentary Disorders and Lentigines

5.1 The Epidemiology of Pollution-Associated Hyperpigmentation

The linkage between environmental pollution and cutaneous hyperpigmentation has been confirmed by the multiple epidemiological reports on diverse populations, but the Asian cohorts have a strong case to make. The multicenter cohort study of 203 Chinese women aged 20-59 years in two cities with varied air pollution levels showed the existence of significant differences between populations with respect to skin chromophores. The index of melanin was much greater in the area of the eye in women in the cities with high air pollution, whereas the value of the b b (yellowness) was increased in the cheek and the eye area in the women of the cities with the middle level of the air pollution. Notably, the same measurements (inner upper arm) which is exposed to air pollutants but not to ultraviolet radiation proved that pollution initiating pigment alterations is independent of the accompanying UV damage, and thus these

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pigment alterations cannot be attributed to UV damage(Bocheva et al., 2023).

The European confirmatory data was given in the landmark SALIA study (Study on the influence of Air pollution on Lung, Inflammation and Aging) where 400 Caucasian women residing in the Ruhr region and Borken in Germany were studied. This clinical cross sectional study showed the significant increase in pigment spots after being exposed to traffic related particulate matter- which proved that hyperpigmentation induced by pollution is not specific to Asians but is a universal phenomenon. On the same note Peng and colleagues performed a clinical cross-sectional study with 400 Chinese women and reported that the exposure to PM2.5 was significantly linked with senile lentigines on the cheeks and hands with average PM 2.5 concentration of 168.13 ug/m3 in Xuanwumen and 63.56 ug/m3 in Yanqing county. These results were further confirmed by Flament and his associates by comparing two cohorts of 102 Chinese women (each) in Baoding (highly polluted city) and Dalian (less polluted city) and showed that the clinical severity of the three signs associated with pigmentation was greatly and significantly increased by the consistent exposure to severe chronic urban pollution. Pigmentary changes occupation-specific have also been reported, where workers in industries where combustion products, tars and heavy metals are used have typical patterns of hyperpigmentation. These professional observations are earlier than the contemporary epidemiological research and are objective proofs of the cutaneous impacts of environmental pollutants(Han et al., 2025).

5.2 Molecular Pathways to Melanogenesis

The molecular pathways of hyperpigmentation caused by pollution all converge on the aryl hydrocarbon receptor (AhR) as a central regulator, which is then followed by the activation of melanogenic pathways by direct and indirect means. To highlight the fact that in addition to exposure to ultraviolet radiation, environmental toxicants also play a major role in the formation of pigment spots during acquisition, Nakamura and colleagues coined the term environment-induced lentigo (EIL) to promote the concept of using AhR signaling activation to emphasize the role of environmental toxicants in pigment spot formation. The up-regulation of tyrosinase by AhR is one of the direct routes of melanogenesis triggered by pollutants. Research has established that, tyrosinase expression and activity is directly induced by AhR activation by environmental ligands, such as polycyclic aromatic hydrocarbon in particulate matter. Investigations on B16F10 mouse melanoma cells showed that AhR is involved in a regulatory process in a-melanocyte-stimulating hormone (a-MSH)-stimulated melanogenesis, and AhR knockdown reduces the amount of tyrosinase activity and melanin after the administration of a-MSH . This defines AhR as a part and parcel of the melanogenic signalling cascade as compared to its functions as a xenobiotic sensor. Nakamura et al. also proved that AhR agonists such as the water-soluble tobacco smoke extract could induce maturation of the melanoblast and AhR activation, which confirms that environmental pollutants directly interact with this pathway. Activation of stem cell factor (SCF)/c-Kit pathway leads to the effect of pollutant on melanogenesis by paracrine signalling. SCF/c-Kit axis plays a critical role in the survival, development and melanogenesis of melanocytes. Nevertheless, in the studies that investigate the effects of PM 2.5 on melanocytes, some complex dose-dependent responses were observed. Suo et al. proved that exposure to PM2.5 had an inhibitory impact on the SCF and basic fibroblast growth factor (bFGF) secretions by keratinocytes in a dose-dependent fashion, and it also reduced melanocyte viability in cases where exposure to PM2.5 is high . These results are indicative that the pigmentation caused by pollution can be a way of establishing a balance between the direct stimulation of melanocytes and the indirect stimulation of melanocytes via the epidermal-melanin unit(Byun, 2025). Another pathway that is considered critical between pollutants and melanogenesis involves oxidative stress stimulation of endothelin-1. Endothelin-1 (EDN1) is a strong melanogenic cytokine, which is synthesized by the keratinocytes upon different stimuli such as the ultraviolet radiation and

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oxidative stress. Grether-Beck clinical trial of the Dusseldorf pollution patch test using 76 participants showed that constitutive skin pigmentation increased with time with transcriptional upregulation of genes that play key roles in de novo melanin synthesis and are activation-dependent on diesel exhaust particles such as POMC, EDN1, MITF, TYR, TYRP1, MLANA, and PMEL. Notably, antioxidant pretreatment suppressed the diesel exhaust particle-induced pigmentation, which supports the envisage the critical role of oxidative stress in mediating such an effect. Keratinocyte to melanocyte paracrine signaling combines the diverse melanogenic signals produced by polluted keratinocytes. The study of Ahn and colleagues involved extensive mechanistic investigation that used normal human primary epidermal melanocytes to establish that particulate matter (5 ug/cm2) raised the concentration of cAMP and protein levels of the Pmel17 / gp100, the subsequent production of melanin by exploiting the endoplasmic reticulum stress signalings arduously by the IRE1a and calreticulin. They also proved that, AhR pathway was involved using particulate matter to boost the CYP1A1 expression. Treatment of melanogenesis in CRT-silenced melanocytes with particulate matter did not stimulate the expression of tyrosinase, which revealed that calreticulin indicates that pollutant-induced melanogenesis involves a critical role of calreticulin. Shi and co-workers validated these results with human epidermal melanocytes who found that PM2.5 raised melanin content and tyrosinase activity in a dose-response relationship with concomitant elevation of melanogenesis proteins. Their ex vivo experiments on human skin and the in vivo experiments on zebrafish embryos affirmed that using PM2.5, pigment area density in tissues was significantly higher than controls(Slominski et al., 2022).

5.3 Clinical Presentation and Differential Diagnosis

Lentigines morphology of pollution-related lesions is slightly different than those of lesions caused by pure sunlight, but there is much overlap. The lentigines caused by pollution normally appear in well-delimited, brown to dark brown lentil-shaped macules, of irregular edges, a few millimeters to more than a centimeter in diameter. They have a smooth and flattened surface; hence, they are different to seborrheic keratoses. Clinical description As a rule, these lesions do not result in symptoms and are essentially cosmetic in nature. Patterns of distribution give valid diagnostic hints on the identification of pigmentation linked to pollution. Although solar lentigines are mostly observed on the areas most exposed to sunlight like the malar eminences, nose bridge, and dorsal hands, the lesions related to pollution show preference to the areas that retain particulate matter especially on the cheeks and forehead. In the Nkengne multicenter cohort study of 203 Chinese women, the melanin index was largely increased in the eyelid locality upon the areas of high pollution, and the periorbital area was possibly especially sensitive to pollutant-induced pigmentation. This distribution reflects not only the patterns of deposition of pollutants but also regional differences in the skin thickness and the barrier function. It is difficult to measure clinically due to the interaction with UV-induced pigmentation, which is often associated with pollution and ultraviolet radiation which both act together and activate melanogenesis(Tímár & Ladányi, 2022). The idea of environment induced lentigo as suggested by Nakamura and his colleagues clearly acknowledges the fact that solar lentigines are caused not by UV alone but by a combination of exposure. Mechanistically, UV and environmental toxicants both stimulate AhR signaling, and induce and maintain a crosstalk among melanocytes, keratinocytes and fibroblasts resulting in the formation and maintenance of lentigines . The interaction has significant implications to prevention and treatment since interventions focused on UV exposure may not be sufficient to deal with the contribution of pollution to hyperpigmentation(Wang et al., 2024). .

5.4 Therapeutic Implications

Antioxidant tyrosinase inhibitors will be a logical treatment of hyperpigmentation caused by pollution, not only of the production of melanin

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but also of the oxidative stress that promotes it. The identification of oxidative stress as mediator of pollutant-induced melanogenesis by several mechanisms, such as AhR stimulation, endothelin-1, and ER, gives a solid argument in support of antioxidants addition to pigment-guided treatment strategies. The Grether-Beck clinical trial showed that antioxidant cocktail of vitamin C, vitamin E and ferulic acid could inhibit the diesel exhaust-induced pigmentation of human skin, which was evidence of the antioxidant potential in preventing pigmentation caused by pollution. The use of clinical formulations with a combination of tyrosinase inhibition with antioxidant activity of a broad spectrum might have benefits over single-mechanism agents in patients with pollution-associated pigmentation. AhR modulation to prevent pigment is a novel treatment option that has been used to regulate the ultimate regulatory of pollutant responses. The direct pollutant effect and paracrine signaling between cutaneous cells through AhR are central and therefore make it an appealing therapeutic target. Investigation showing that AhR stimulation by environmental poisonants provokes melanogenesis in both genomic and non-genomic mechanisms indicates that AhR opponent or regulators may inhibit pigmentation caused by pollution. An AhR-modulating agent, such as tapinarof, already approved to treat psoriasis is also a potential therapeutic candidate, even though its use in treating pigmentation caused by pollution remains unresearched. It is impossible to overestimate the role of early intervention when it comes to the treatment of pigmentary disorders of a pollution-related nature(Li, Kuai, Cui, & Miao, 2022). The advancement of the damage caused by pollutants, along with the self-stimulating processes of oxidative stress and inflammation, implies that the stable hyperpigmentation can become more stubborn with time. The idea of an oxinflammatory memory suggested in this review i.e. temporary exposure to pollution triggers lasting cellular changes due to epigenetic changes and metabolic reprogramming is especially applicable to pigmentation. After the melanin has been deposited in the dermis due to the chronic stimulation of melanocytes that have been damaged by the disruption of basement membrane, the reversal is significantly harder. The clinical evidence that antioxidant pre-treatment can inhibit pigmentation due to the diesel exhaust particle is an important indication of the significance of pre-treating at-risk populations in clinical environments. In patients who live or travel to high-pollution areas, it is possible to consider introducing antioxidant and barrier-protective protocols into the routine use of skincare as early as possible to forestall the development of long-lasting hyperpigmentation that will be recalcitrant to subsequent intervention.

6. Clinical Manifestation 3: Wrinkle Formation and Premature Aging

6.1 Epidemiological Evidence for Pollution-Induced Aging

The cause and effect relationship between environmental pollution and cutaneous aging has been well established by pioneering epidemiological research across continents and groups. The German SALIA cohort (Study on the influence of Air pollution on Lung, Inflammation and Aging) is the pioneer study in the area, having cohort followed hundreds of older women to explain the association between air pollution exposure and phenotypes of skin aging. Researchers were able to demonstrate that exposure to traffic-related particulate matter was an important factor in promoting wrinkle formation among 806 Caucasian women aged 66-79 years, regardless of ultraviolet radiation exposure, smoking history, and other confounding factors in a seminal analysis of this group. The advantage of the SALIA study is that it utilizes the validated SCINEXAtm (SCore for INtrinsic and EXtrinsic skin Aging) scoring system, which makes it possible to objectively measure the extrinsic aging features such as rough wrinkles and pigment spots. Later validation experiments have shown that these results are replicated in the Asian populations, and wrinkling brought about by pollution is a global phenomenon and not something unique to a particular ethnic group. In the present

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retrospective study, 389 Taiwanese patients aged 30-74 years were studied with the help of the VISIA Complexion Analysis System, during which the wrinkles, texture, and pores of the skin were objectively measured and their values correlated with the address-specific air pollution data provided by monitoring stations. The findings indicated that exposure to non-methane hydrocarbons (NMHC) had strong correlations with adverse scores on skin texture, and counterintuitive results that showed ozone exposure had positive correlations with texture and pore scores, highlighting the complexity of the effect of pollutants on the skin texture. Notably, this research also established that carbon monoxide, NMHC, nitrogen dioxide, nitrogen oxides, particulate matter (PM2.5 and PM10), and sulfur dioxide had a significant impact on skin condition in people above 45 years of age; hence, older skin is more susceptible to effects of pollutants on skin. The dose-response relationships would create the most compelling evidence of causality of skin aging related to pollution(Denisow-Pietrzyk, 2021). The researchers of the SALIA study discovered that the forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of the lung functional outcome was reduced by 1.2 per cent of the 6-point rise in the wrinkle severity score, when the investigators have controlled age, education level, body mass index, and skin type as well as sun exposure. The correlation between the skin and lung aging was powerful and not depended on smoking or air pollution, which implied that both organs were similar in terms of vulnerability to environmental offenses. Moreover, dose-response relationships between ozone and wrinkles coarse were independently validated in two German cohorts (SALIA and BASE-II) with positive relationships in both cohorts and in the combined sample, irrespective of chronic exposure to ultraviolet radiations and co-pollutants, including particulate matter and nitrogen dioxide. These results show that chronic exposure to higher levels of troposphereic ozone causes skin aging in a quantitative manner with cumulative exposure having a linear relationship with the severity of wrinkles. Ecological validity has been introduced into these epidemiological observations through real-life exposure studies. A 2024 study of 124 women in Paris over six months monitored individualized exposures to pollutants by using smartphone GPS tracking attached to the Breezometer platform. An elevated cumulative exposure of PM10 had a significant relation with more wrinkles and roughness under the eye, whereas exposure to lower air quality had a significant relation with more forehead wrinkles and less elasticity of the skin . This is a real time and real-world methodology which proves the associations of controlled cohort studies to be applicable to daily life circumstances(Ferrara et al., 2021).

6.2 Extracellular Matrix Degradation Mechanisms

The pathophysiology of the formation of wrinkles by pollution involves the destruction of the components of the dermal extracellular matrix, especially of collagen and elastin by the effects of the matrix metalloproteinases (MMPs). PM causes a series of events which cause MMP induction, resulting in an imbalance between matrix synthesis and degradation that gradually undermines dermal architecture. The induction of matrix metalloprotease (MMP) is the primary pathway that the exposure to the pollutants leads to the loss of the collagen. It has been shown that PM exposure enhances the synthesis of reactive oxygen species (ROS) including superoxide and hydroxyl radical, which also appear to increase production of MMPs including MMP-1, MMP-2, and MMP-9 (Xiao et al., 2023). The result of this oxidative stress-mediated induction of MMP is the loss of collagen which is the major structural protein of the dermis and this leads to the clinical effects of skin aging. The relationship between pollutant exposure and MMP expression is strong enough to declare the genetic variants of MMP promoters as susceptibility factors in aging due to pollution. The SALIA cohort study demonstrated that wrinkles in the skin were only associated with a decline in lung function in the carriers of the MMP-1 2G (rs1799750) or the MMP-3 6A (rs3025058) allele as opposed to the homozygous carriers of 1G allele or the homozygote of the 5A

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allele. These alleles seem to represent a shared genetic vulnerability to aging of tissues due to environmental influence, which is why gene-environment interactions would be valuable in individual risk determination. In matrix degradation caused by pollution, MMP-1 (collagenase-1) is a specific and essential pathway that is upregulated by AP-1 and NF-kB. MMP-1 triggers degradation of the native fibrillar collagens type I and III by cleaving the collagen molecules at a particular site to result in fragments which denature at the body temperature and become vulnerable to further proteolysis by gelatinases like MMP-9. The transcriptional increase of the MMP-1 after exposure to the pollutants is induced by transcriptional factors activator protein-1 (AP-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) that are triggered by the oxidative stress produced during the metabolism of the pollutants . This is the route that makes a direct mechanistic connection between the oxidative stress in Section 3 and the ultimate clinical outcome wrinkle formation. The subsequent dermal degradation caused by MMP-9 (gelatinase) activation and destruction of basement membrane damages both denatured collagen fragments (gelatin) and type IV collagen which is a significant constituent of the basement membrane at the dermalepidermal junction. Damage of this zone of the basement membrane compromises the structural integrity of the skin and could promote the downward mobility of melanocytes or melanin pigment, which is part of the pigmentary alterations in Section 5. A combination of various MMPs with collagenases to begin cuts, gelatinases to finish degradation, is necessary to cause an efficient removal of damaged matrix components, but with chronic activation leads to net matrix loss. The final destiny of the dermal collagen depends on the imbalance between the MMPs and the tissue inhibitors (TIMPs). The presence of Tissue inhibitors of metalloproteinases (TIMPs) usually balances that of MMPs to ensure that there is homeostatic turnover of extra cellular matrix. Exposure to pollution interferes with this balance by stimulating MMPs in an uneven manner in comparison with TIMPs, moving the balance toward degradation. This ratio is worsened by the disruption of the production of new collagen in the next section and results in a two-fold process of net matrix degradation: increased degradation and insufficient replacement(E. Liu, Xue, Li, & Liao, 2025).

6.3 Impaired Extracellular Matrix Synthesis

Although degradation mediated by MMPs eliminates the existing collagen, pollution is also capable of inhibiting the production of new extracellular matrix components that cause a dual deficit, leading to faster dermal atrophy and wrinkle development. Fibroblast senescence, decreased collagen synthesis is one of the core processes of aging under the influence of pollution. The main mesenchymal cells, the fibroblasts, that are involved in the production of collagen, elastin and other parts of the matrix are prematurely senesced after being subjected to oxidative stress. Senescent fibroblasts have a lower proliferation capacity and the decreased production of collagen and at the same time have gained the senescence-associated secretory phenotype (SASP), which is characterized by the secretion of pro-inflammatory cytokines and the additional production of MMPs that further degenerate the extracellular matrix. This switch to a catabolic condition as a result of productive matrix synthesis is a threshold event in the aging process induced by pollution and beyond it, architectural changes become more and more irreversible. The mechanism of inhibited collagen synthesis after exposure to pollutants has a mechanistic explanation based on TGF-b / Smad pathway(Stoykova, Koycheva, Binev, Mihaylova, & Georgiev, 2025). The major signaling pathway that stimulates collagen gene express in dermal fibroblasts is to transform the growth factor-beta (TGF-b) cue by using Smad transcription factors. The studies on UVB-mediated premature senescence have established that TGF-b1 is causal in stress-mediated senescence and neutralization of TGF-b1 antibodies or its receptor II significantly suppressed senescence-related features. Latent and active TGF-b1 are both enhanced after oxidative stress and it is possible that dysfunction of this pathway is one contributor

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to the environmentally-aged skin phenotype of fibroblasts. This study was on UVB exposure, but since the mechanism of oxidative stress is similar with that of pollution exposure, it is possible to have similar TGF-b dysregulation after an insult of pollutant. This is aggravated by altered deposition of elastin and fibrillin which affect the skin elasticity and recoil. The elastin fibers are made of an elastin core which is surrounded by fibrillin-based microfibrils which give the skin its ability to deform and get back to its original shape. The oxidative stress that results due to pollution damages the already existing elastic fibers and at the same time interferes with the synthesis of new elastin and fibrillin by senescent fibroblasts. The outcome is a gradual decrease in elasticity, which is clinically felt as skin laxity and slow recoil on stretching of the skin. This relationship was confirmed by the Paris real-life exposure study which showed that exposure to lower air quality was associated with the reduction of the skin elasticity in objective biophysical measurements.

6.4 Clinical Features of Pollution-Aged Skin

The clinical phenotype of the skin aging caused by pollution is characterized by some typical features, which distinguish it, at least partially, with chronological or photoaging phenotypes. Coarse topography of wrinkle is the most apparent indication of dermal degradation caused by pollution. In contrast to the fine rhytides that come with chronological aging or with deep furrowing of the skin seen in extreme photoaging, pollution-related wrinkles tend to appear as larger irregular lines spread out on the face. It was observed in the ozone studies of the German cohorts that relationships were observed with the presence of coarse wrinkles on the face and not fine lines. This topography is an expression of a pattern of underlying matrix degradation, whereby loss of the dermal support results in the development of the gravitational folds and expression lines increasing in intensity. The forehead wrinkles seem especially sensitive to pollution exposure, and the real life study in Paris has reported certain relations between the poor air quality and the severity of forehead wrinkles in the individuals.

Wrinkles are accompanied by the loss of the elasticity and firmness of the skin as the dermal matrix loses its architecture. The cutometry is the measurement of the elasticity most commonly done to assess the capacity of the skin to resume its initial position following deformation. The Paris experiment had strong records of negative relationships between air quality and reduction of elasticity of the skin, thus verifying that exposure to pollutants inhibits the biomechanical characteristics of skin . This loss of rigor is the degradation of collagen (which creates tensile strength) and destruction of elastin (which creates recoil) and an effect is a sagging and inability of the skin to regain its own shape after being stretched or compressed. The clinical triad of aging due to pollution is complete with texture abnormalities(Lee et al., 2024). Skin texture The fine structure of skin surface markings is evenly coarse and irregular after exposure to pollutants. The Taiwanese VISIA study showed that there were strong correlations between the NMHC exposure and adverse texture scores and the quantitative measurements proved that this parameter deteriorates. Likewise, the Paris research concluded that the more PM2.5 and PM10 the rougher under the eye which is a sensitive part since the skin is thin and visible. Contravention of texture indicates epidermal (dropped differentiation and turnover of the keratinocytes) and dermal (depletion of the supportive matrix to support surface topography) alterations. These coarseness wrinkles, loss of elasticity and weakening of texture gives the appearance of old age which is the characteristic of prolonged exposure to polluted environments.

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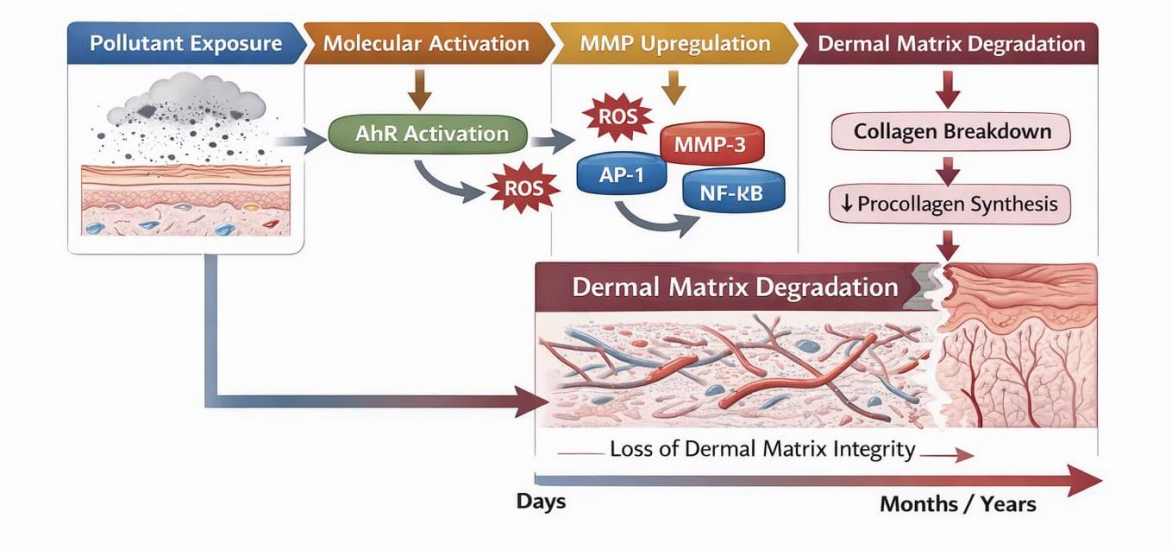


FIGURE 2: The Pollution-Induced Extracellular Matrix Degradation Cascade

Pollutants (PM-bound PAHs) penetrate skin → activate AhR and generate ROS → trigger AP-1 and NF-κB transcription factors → upregulate MMP-1, MMP-3, MMP-9 and suppress procollagen synthesis → chronic imbalance of collagen degradation over production → progressive dermal matrix loss over months to years → clinical wrinkle formation once structural support fails.

7. Interactive Effects: Pollution Plus Ultraviolet Radiation

7.1 The "Photo-Pollution" Synergy Concept

Ultraviolet radiation and air pollution are not independent insults to the skin, but they interact in a complex, synergistic manner to increase cutaneous damage beyond that which would be expected in the presence of the simple effects. This effect which is also commonly called photo-pollution is a major factor to ponder on in the real-life skin damage in the environment, as in urban settings, humans are always exposed to both of these factors together. This synergy is based on shared signaling pathways. Aryl hydrocarbon receptor (AhR) is the common molecular target of both the pollutants and ultraviolet radiation but in different ways. Direct ligand agonists of AhR on cutaneous penetration of particulate matter are pollutants, especially polycyclic aromatic hydrocarbons (PAHs) that are adsorbed to particulate matter. At the same time, UV radiation, i.e. UVB produces highly potent AhR ligands by photochemical transformation of an endogenous amino acid, tryptophan, to 6-formylindolo[3,2-b]carbazole (FICZ), a compound with an extremely high affinity to the receptor. The combination of these two in AhR forms a hyperstimulated signal: the pollutant-produced ligands and UV-produced FICZ can stimulate the same group of receptors, leading to increased expression of the cytochrome P450 enzymes (CYP1A1, CYP1B1) and the cascade of oxidative stress and the production of inflammatory mediators as mentioned in the previous sections(Pambianchi, 2021). Intermediate downstream mechanisms, including the activation of NF-kB, the induction of matrix metalloproteases, the production of pro-inflammatory cytokines, etc., are accordingly overactivated when they are exposed together. The amplification effect of damage beyond additive effects is clearly proven by mechanistic studies of mitochondrial toxicity. Studies by Larnac et al. have shown that benzo[a]pyrene (BaP), which is the most common PAH due to incomplete burning of organic materials, has a high affinity towards mitochondria and the affinity causes severe induction of lipid peroxidation and membrane disruption when the body is subjected to UVA light in combination with the androgenic

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substance (BaP). The synergistic effects of Co-exposure to UVA and BaP are deteriorating mitochondrial membrane potential, mitochondrial metabolism, and integrity of the mitochondrial network. Such mitochondrial synergy has far-reaching implications on the aging of the skin because mitochondria are the targets and sources of oxidative stress, and their dysfunction is the direct cause of the so-called oxinflammatory memory phenomenon discussed in this review. The aforementioned study by Larnac et al. in Nature Scientific Reports further revealed that UV and urban particulate matter concomitant exposure causes oxidative stress, mitochondrial damage, DNA damage, senescence, and apoptosis in human melanocytes and skin explants exhibited typical aging characteristics such as epidermal thinning, barrier damage, fibrosis, and changed pigmentation. These mechanistic findings are clinically relevant as evidenced by epidemiological evidence of interaction. An 83-volunteer cross-sectional study found that the risk of getting wrinkles was 11.4 times greater when there was concomitant exposure to excessive sun exposure and heavy smoking (a concentrated source of PAHs) as compared to non-smokers or those who had less than two hours of sun exposure per day. This multiplicative effect of increase is greater than population-level confirmation of the synergy of photo-pollution. Likewise, a series of research studies investigating the response of ozone and UV co-exposure using 3D pigmented living skin equivalent models has shown that co-exposure produced a strong effect in enhancing darkening of the skin surface relative to either of the stressors and transcriptomic analysis indicated that the stressors worked in concert on genes that regulate skin barrier functionalities, chronic inflammatory effectors, and apoptotic signaling pathways(Llewellyn et al., 2022).

7.2 Mechanistic Basis of Synergy

The pollutant ligand enhancement and the AhR activation to UV works in a complementary manner. Although one of the sources of AhR activation is UV-generated FICZ, ultraviolet radiation also increases the strength of pollutant-derived ligands. PAHs may also be chromophores, by absorbing UVA photons because of the conjugated aromatic ring structures. Even the PAHs with five or more aromatic rings can absorb visible light. When PAHs absorb photons, excited-state PAHs become excited and dissipate electrons or energy into molecular oxygen or other biomolecules to produce reactive oxygen species such as singlet oxygen (1O2) and superoxide anion (O2 -). This activation is a photochemical activation of the relatively non-toxic PAH molecules into a powerful source of oxidative stress, making them more toxic at otherwise sub-toxic concentrations. A second mechanism of amplification is photochemical production of more ROS. The photoexcited PAHs cause reactions, which generate large amounts of reactive oxygen species that react with cell components such as lipids (lipid peroxidation), proteins (carbonylation), and DNA (8-hydroxy-2'-deoxyguanosine formation and strand breaks) . Experiments with HaCaT keratinocytes have shown that low concentrations of PAH (10-9 to 10-7 mol/L; containing naphthalene, phenanthrene, pyrene and benzo[a]pyrene) together with UVA irradiation can lead to histone H2AX phosphorylation, indicative of the induction of DNA damage, and that DNA strand breaks are detectably induced at higher concentrations. The lowest concentration of the phototoxic particle matter organic extract was 1.8 mg/ ml, and the lowest concentration of the phototoxic particle matter was 25mg/ ml which is applicable in the real-life exposure condition(Y. Zhu et al., 2021).

Under combined exposure, oxidative damage is caused by depletion of shared antioxidant defenses. An intricate complex of enzymatic and non-enzymatic antioxidants is present in the stratum corneum and they normally neutralize reactive species. Ozone, a powerful gaseous pollutant, directly removes vitamin E, Vitamin C and glutathione in the stratum corneum. These antioxidants are also destroyed by ultraviolet radiation by photochemical reaction. When the two stressors operate in concert, the depletion of the antioxidants would proceed faster leaving the skin exposed to oxidative damage which would otherwise be regulated. This loss is especially true

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of the surface lipid squalene, whose oxidative stress biomarkers, as well as agents of inflammation and comedogenicity, are peroxidation products of this lipid. The synergistic cycle is completed by greater penetration of the pollutants following the damage to the barrier caused by UV. Both acute and chronic UV exposure affect the integrity of skin barriers in several different ways: loss of natural moisturizing factors, tight junction protein disruption and lipid organization changes in the stratum corneum. This barrier invasion eases the increased intrusion of particulate matter, PAHs, and other pollutants into the viable epidermis and dermis, where they may communicate with living cells and produce further harm. The weakened barrier also allows more UV radiation to penetrate it in itself, since the optical characteristics of stratum corneum are changed as well, which forms a feed-forward mechanism of a progressive damage(Yu et al., 2024).

7.3 Clinical Implications of Combined Exposure

The most clinically relevant effect of photo-pollution synergy would be accelerated aging of skin exposed to the sun and pollution. The interactions of the stressors act on epidermal and dermal compartments, inducing the collagen degradation via matrix metalloproteinase and the lack of synthesis in Section 6 and the melanocyte malfunction and pigment alteration in Section 5 at the same time. Combined exposure can lead to mitochondrial damage that is potentially especially important because mitochondrial dysfunction has been observed to cause premature skin aging by disrupting cellular energetics, by propagating low levels of ROS, and by triggering cellular senescence. In recent clinical studies, reduction in the ATP levels of the stratum corneum in people who have suffered urban pollution and reduced mitochondrial DNA in the blood cells have been noted, which is an indication of systemic consequences of mitochondrial damage as a result of the pollution. The consequences of the photoprotection strategies are far-reaching and require the transformation of the historical UV-only strategies(Rahimi et al., 2025). Although conventional sunscreens play a critical role in avoiding the losses caused by UV rays, they do not provide the maximum protection against photo-pollution unless they are specially prepared by using the necessary additional ingredients. The identification that UVA1 wavelengths (340-400 nm) are specifically significant in PAH phototoxicity activation, highlights why it is important to have broad-spectrum products with high UVA1 protection factor. In addition, the use of photoprotection should be complemented with antioxidant measures to respond to the oxidative aspect of the photo-pollution damage. The antioxidant formulations in Section 8 (especially those with vitamin C and E with ferulic acid) have shown to be effective in preventing pollutant-induced pigmentation and barrier disruption in controlled human experiments and would also have a logical effect on counteracting the photo-pollution synergy, albeit specific combination studies are required. The requirement to have a holistic exposome protection not only on topical products but on holistic provisions to cover the entire gamut of environmental exposures. Multi-benefit photoprotection is a concept that has emerged, in which not solely UV filters are used but also film-forming polymers that form physical barriers to the deposition of particulate matter, antioxidants that counteract the effects of pollutants on the skin, and ingredients that facilitate the intrinsic detoxification mechanisms of the skin especially via the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor. Systemic support of cutaneous defenses by oral supplementation with antioxidants including Polypodium leucotomos, carotenoids and polyphenols may be developed but the evidence of pollution-specific effects is yet to be fully developed. Due to the ongoing urbanization and the exposure to pollution that is nearly everywhere, the addition of the exposome-wide protection into the everyday skincare is no longer a cosmetic issue but a health preventative necessity(Proietti, Guida, Dybala, Spagnoli, & Potenza, 2024).

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[TABLE 3: Comparative Analysis of UV and Pollution-Induced Skin Damage]

Parameter	UV Radiation	Air Pollution (PM/PAHs)	Combined Exposure (UV + Pollution)
Primary Chromophore/Receptor	DNA, chromophores, AhR	AhR, surface lipids	Both (synergistic activation)
ROS Generation	High (immediate)	Moderate (sustained)	Very high (amplified)
AhR Activation	Direct (via UV photoproducts)	Direct (via PAH ligands)	Synergistic
DNA Damage	Cyclobutane pyrimidine dimers	Bulky adducts, 8-oxo-dG	Multiple lesion types
MMP Induction	High	Moderate	Supra-additive
Pigmentary Response	Delayed tanning	Direct melanogenesis	Enhanced pigmentation
Barrier Disruption	Acute (immediate)	Chronic (progressive)	Accelerated
Clinical Time Course	Acute and chronic	Primarily chronic	Accelerated chronic

8. Therapeutic Interventions: From Preclinical Promise to Clinical Proof

8.1 Establishing Clinical Evidence Standards for Pollution-Protection Claims

The break-neck growth in the skincare sector of the so-called anti-pollution market has exceeded the standardization of regulatory systems to assess the way products work, so that in this position the marketing assertions usually far outstripped the evidence they purport to support. Such lack of correspondence between commercial and scientific validation makes it very difficult to dermatologists who need to prescribe evidence-based interventions to patients who are worried about environmental skin damage. The increase in products that claim to protect against pollution, frequently relying on scanty in vitro data or convoluted mechanistic arguments, highlights the desperation of demanding high standards of clinical evidence that would help not only in developing products but also in recommending their use in the clinic. Regulatory requirements and marketing statements are two standards of proof that are entirely different and clinicians and consumers should juggle with. The regulatory bodies such as U.S. food and drug administration and European Medicines Agency demand strict clinical trial records that prove safety and effectiveness before they accept pharmaceutical interventions(Benedusi, Frigato, Bertolucci, & Valacchi, 2021). However, cosmetic products are regulated by other regulations that are more restrictive on the manufacturers to substantiate claims and do not require specific testing conditions. This regulatory loophole has allowed an increase in products being sold as anti-pollution against the basis of in vitro data or surrogate endpoint that may not be translated to bring about clinically significant benefit upon exposure in the real world. There are significant regulatory implications of the difference between preventive and curative claims. Claims to prevention- Preventive claims that a product helps prevent damage caused by pollutants must be shown to have increased barrier functionality or antioxidant capability or decreased penetration of pollutants. Claims Curative claims- that a product can reverse the damage of existing pollution-require demonstrations of clinical benefits in such endpoints as the severity of the wrinkles, pigmentation or elasticity of the skin after the intervention. The two types of claims require solid study designs with suitable controls, validated measures of outcome, and statistically powerful sample sizes.

Human data requirement in actual exposure conditions of a pollutant has become a guiding principle in developing clinical credibility of a pollution-protection product. Although in vitro studies on cultured cells or ex vivo related skin tissues are informative on the mechanism of action and can be effective screening tools in

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investigating a product, they do not reflect the complexity of human skin or the multidimensionality of a real-world exposure to pollutants. The human skin has highly anatomical, immunological, and metabolic peculiarities, which affect the interactions of pollutants in a manner that cannot be fully reproduced in simplified model systems. The intermediate level of evidence provided by controlled human exposure studies, in which volunteers are exposed to specified pollutant concentrations in the laboratory setting, provides intermediate evidence between mechanistic investigation and clinical application. An example is the Dusseldorf Air Pollution Patch Test which relies on repeated exposure to diesel exhaust particles to specific regions of the skin, and allows quantitative determination of pigmentation, barrier effects, and inflammatory activity in the presence and absence of test product application under controlled conditions. This method manages confounding variables that would have been present in reality studies but still relates to human physiology. In the best case scenario, clinical studies must include real-world exposure measurement with personal monitoring devices which are used to measure the individual exposure to pollutants over time. The recent Paris experiment with smartphone GPS tracking coupled with air quality services is a good example of such a strategy as it shows the correlation between personalized exposure to PM10 and objective skin parameters such as wrinkles, roughness, and elasticity quantified by standardized biophysical methods. These methods can be used to assess product efficacy in conditions of actual exposure and to consider individual differences in exposure to pollutants, activity, and environmental context. The adoption of personal exposure check with clinical outcome evaluation is the best standard in determination of product efficacy in pollution protection. Another important factor in generation of evidence of pollution-protection products is surrogate endpoints and their validation. Quantifiable endpoints, such as squalene peroxidation products (SQOOH), protein carbonyl, 8-hydroxy-2'-deoxyguanosine (8-oxo-dG), and inflammatory cytokines, are biomarkers of damage caused by pollution that can be measured immediately after a short-term exposure, making these biomarkers more efficient in designing clinical trials than pain and pigmentation changes in wrinkles. Such surrogate endpoints must be proven to be correlated with clinically meaningful effects like wrinkle formation, pigmentation or barrier dysfunction in the longer period. Their inclusion in clinical studies has been made easy by the development of standardized procedures at collecting and analyzing them, such as tape stripping of stratum corneum in sampling sebum to analyze lipids and minimal invasive biopsy procedures to analyze the tissues, among others. The relationship between products of the squalene peroxidation and the eventual pigmentation alterations, such as, justifies the use of the biomarker as a surrogate endpoint in clinical trials aimed at pigment preventive measures(Nemade, Baste, Bihani, & Raut, 2025).

8.2 Topical Antioxidants: The First Line of Defense

Topical antioxidants are the best-investigated and clinically approved intervention that can help to prevent the damage of skin caused by pollution. Their explanation is based directly on the key role of oxidative stress in the pathogenesis of pollutants determined in Section 3: by preventing the occurrence of reactive oxygen species prior to their ability to damage cellular components, antioxidants break the pathway of events leading to inflammation, matrix damages and pigmentary alterations. The use of topical antioxidants as first-line defense against environmental skin damage is a strong indicator of the soundness of the mechanistic explanation and of the growing body of clinical support to the efficacy of this approach. Vitamin C (ascorbic acid) is the keystone of the best topical antioxidant practice because of its multiplicity of tool purposes in the field of cutaneous biology and the fact that it is not produced by humans and must be provided in exogenous sources. Ascorbic acid being a strong reducing agent gives up the electrons to neutralize the free radicals such as superoxide anion, hydroxyl radical and singlet oxygen, produced

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during pollutants exposure. In addition to its direct radical scavenging effect, vitamin C restores oxidized vitamin E, which allows synergistic antioxidant protection at lipid-aqueous interface of lipid-bound cell membranes, and is a fundamental cofactor to prolyl and lysyl hydroxylases needed to produce collagen. This antioxidant and collagen-supporting dual activity is what renders vitamin C especially appealing, in regards to facial aging caused by pollution, which is a combination of both oxidative stress and matrix remodeling. The clinical studies of the efficacy of vitamin C in pollution prevention are based on controlled human studies, which proved the effect of pretreatment with 15% L-ascorbic acid in preventing lipid peroxidation effect by pollutants, upsurge of inflammatory markers and collagen destruction. The Ferrara exposure model based on multipollutant (UV + ozone + diesel exhaust) showed that the loss of keratin 10, desmocollin and claudin proteins either vital to the epidermal structure and epidermal barrier or damage to inflammasomes, assessed by NLRP1/ASC-co-localization, was strongly prevented by vitamin C-based formulations. These results prove that vitamin C can prevent a variety of factors of pollutant-induced cutaneous dysfunction instead of acting as an antioxidant. Topical application of vitamin C has serious problems to formulate since it is not stable in aqueous solutions where it is readily oxidized to inactive dehydroascorbic acid. To stabilize the molecule, the formulations should have a low pH (less than 3.5) to ensure that the patient finds it easy to take, and use a packaging that eliminates light and air that may result in degradation during storage. These considerations during the formulation are not just technical facts but vital determinants of clinical efficacy because poor vitamin C is not able to deliver the desired antioxidant effects. The lipophilic character of vitamin E (tocopherol) complements the hydrophilic protein of vitamin C, allowing it to inhibit lipid peroxidation chain reactions by donating a hydrogen atom to membrane lipid oxidants, blocking the spread of oxidative damage via lipid peroxidation through membrane lipids. a-Tocopherol, the most active form, is the lipophilic antioxidant that prevents the continuation of oxidative damage by lipids through the membrane lipid. It is also important to note that this role of membrane-protectant is especially applicable to pollution protection, because the lipid peroxidation products, such as squalene peroxides, can be used as bioindicators of exposure, as well as intermediates of both inflammatory and comedogenic actions. It has been clearly demonstrated that vitamin C and vitamin E interact synergistically: vitamin C will restore oxidized vitamin E on the membrane surface, allowing the antioxidant to be maintained further by what has been known as the antioxidant network. This synergy is the basis of the increased effect that the combination of the formulations is superior to the activity of the vitamins themselves and offers a mechanistic explanation as to why they should be used together(Ivarsson, Pambianchi, Pecorelli, Lim, & Valacchi, 2025).

Ferulic acid can be used as an antioxidant ingredient as it is a direct radical scavenger, and also it protects the vitamin C against oxidation. It is a phenolic plant cell wall product that absorbs ultraviolet radiation and removes the free radicals produced in the course of photo-oxidative stress. Its inclusion in vitamin C + E formulations gives it about twice the photoprotection of the vitamins alone, as determined by the protection against erythema and cell sunburn. In pollution protection, ferulic acid adds to the total antioxidant activity of the combination formulae as seen in CF Mix experiments, and the UV-absorbing properties of ferulic acid are also an added value in photo-pollution synergy discussed in Section 7. Multi-ingredient solutions to pollution protection have been shown to be more effective than single antioxidants in a variety of clinical trials, thus explaining the efficacy of combination formulations. The difference between additive effects and synergistic interactions applies not only to vitamin C regenerating oxidized vitamin E but also to ferulic acid stabilizing vitamin C and each antioxidant attacking different cellular locales and reactive species. This multi-targeted strategy is consistent with the multi-faceted characteristics of the oxidative stress caused by pollution, including

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lipid peroxidation, protein carbonylation, DNA oxidation, as well as an activation of inflammatory signaling cascades. The clinical trial results of certain combination formulations, specifically CF Mix, have the greatest evidence base of topical use of antioxidants in pollution prevention(Prieux, 2021).

8.3 Clinically-Validated Antioxidant Formulations

The CF Mix (15% ascorbic acid, 1 percent tocopherol, 0.5 percent ferulic acid) is the most researched topical antioxidant formula in terms of pollution protection and several controlled human studies have shown its ability to counter various stresses in the environment. This particular formulation, comprised of developing the ascorbic acid in pH < 3.5 so as to achieve stability and penetration, has been tested in both the controlled laboratory environment and the environment in reality. The choice of the particular concentrations: 15% ascorbic acid, which is the saturation of cutaneous absorption, 1 percent tocopherol, which is the best lipid-phase antioxidant activity, and 0.5 percent ferulic acid, the maximum enhancement of stability, is decades of formulation science at its highest point optimization of delivery and efficacy(Sikora, Wortzman, Nelson, & Dover, 2021). Controlled human exposures obtained evidence forms a strong support of CF Mix efficacy in the context of damages caused by pollutants. The 4-day single-blinded clinical test of Ferrara and colleagues was carried out on a total of 15 female subjects on their backs using a strictly designed protocol: test zones were treated on a daily basis with or without CF Mix, representing the participant to 2 hours of exposure to particulate matter followed by 5 minutes of exposure to ultraviolet radiation. This design facilitated the ability to evaluate product efficacy as compared to mixed pollutant+ UV stress that occurs in real-life urban environment and adjust for individual variation in tests and environmental confounding. The immunohistochemical analysis of protein expression change used in the study to determine the effect of the formulation on clinical scores other than providing clinical scoring alone, offers mechanistic understanding of the protective action of the formulation at the molecular level. PM + UV-induced barrier disruption was prevented by using the immunohistochemical method to detect major epidermal protein required in stratum corneum integrity and functionality. The loss of involucrin and loricrin as two crucial constituents of the cornified envelope to retain the stratum corneum structural integrity and to give the scaffold on which the lipids are organized was prevented by CF Mix pretreatment. Protective effects of barriers were also supported by maintenance of normal patterns of differentiation of keratinocytes and inhibition of morphological alterations of cell exposure to pollutants, such as cell disorganization and spongiosis. These results were corroborated by the Ferrara multipollutant study which revealed that the AOX mix inhibited the depletion of keratin 10 (a keratinocyte differentiation marker), desmocollin (a desmosomal protein crucial in cell-cell adhesion), and claudin (a tight junction protein that controls paracellular permeability) in response to combined exposure AOX and UV, ozone and diesel exhaust. This is a holistic maintenance of epidermal structure mechanistic explanation of the clinical finding that antioxidant pretreatment decreases transepidermal water loss and skin hydration during exposure to pollution. Aggression of the elimination of collagen and activation of MMPs will deal with the underlying mechanism of wrinkle generation by pollution, which proves that the antioxidant protection framework is not limited to the epidermis to maintain dermal matrix integrity(Moneo-Sánchez et al., 2024). Immunohistochemical examination showed that CF Mix pretreatment inhibited the decrease in type I collagen staining in untreated, pollutant-exposed skin which showed the presence of primary structural protein of the dermis. At the same time, the formulation prevented the increase in matrix metalloproteinase-9 (MMP-9) the gelatinase that breaks down denatured collagen fragments formed by the cleavage of MMP-1. The overall restoration of collagen production and inhibited breakdown offers mechanistic clarification of the anti-aging results with regular intake of antioxidants and the clinical suggestion

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of daily use of antioxidants to patients who fear aging by pollution reasons. These findings were then expanded by the Ferrara multipollutant study, which showed that the AOX mix prevented the activation of the NLRP1 inflammasome, as measured by the co-localization of ASC, and had no impact on aquaporin 3 expression, a key expression necessary in epidermal water homeostasis. These findings confirm that antioxidant pretreatment prevents various elements of pollutant-induced cutaneous dysfunction, such as damage to the barrier, inflammation, and dehydration, which justifies the use of such formulations as overall first-line prevention of environmental skin damage(Konisky, Bowe, Yang, & Kobets, 2023).

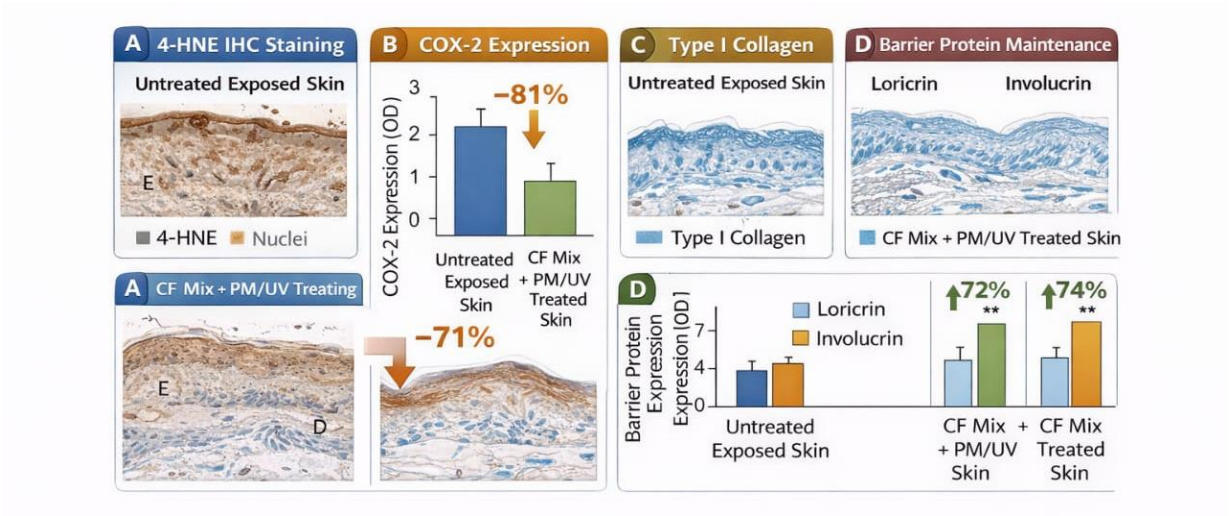


Figure 3: Clinical Efficacy of Topical Antioxidant Serum Against Pollution-Induced Damage

(Data from a 4-day single-blinded clinical trial (n-15) evaluating a totopical formulation containing 15% ascorbic acid, 1% tocopherol, and 0.5% ferulic acid (CF Mix) against combined PM and UV exposure. (A) immunohistochemical staining for 4-hydroxynonenal (lipid peroxidation marker) shows marked reduction in treated sites. (E) Quantification of COX-2 expres-sion demonstrates significant inhibition of inflammatory responses. (C) Type I collagen preservation in CF Mix treated ver-sus untreated exposed skin. (D) Barrier protein (loricrin, involucrin) maintenance with antioxidant pretreatement. Adapted from Ferrara et al., 2024)

8.4 Targeted Pigment Prevention Strategies

Even Tone Serum clinical trial (Dusseldorf Air Pollution Patch Test) presented direct data that topical antioxidants have the ability to inhibit pollutant-induced pigmentation by a mechanism that is independent of their overall antioxidant activities. Grether-Beck clinical trials of Dusseldorf pollution patch test on 76 people showed that constitutive skin pigmentation in given areas rose time-dependingly when diesel exhaust particles were regularly applied using quantitative chromametry. This hyperpigmentation was also accompanied by transcriptional upregulation of genes necessary in de novo melanin synthesis such as POMC (proopiomelanocortin, the precursor of melanocyte-stimulating hormone), EDN1 (endothelin-1, a powerful melanogenic cytokine), MITF (microphthalmia-associated transcription factor, the master regulator of melanocyte differentiation), TYR (tyrosinase, the rate-limiting melanin synthesis enzym This transcriptional orchestration suggests that exposure to pollutants actively triggers melanogenic programming as opposed to allowing passive pigmentation to occur(Nie, Hou, & Li, 2025).

Antioxidant pretreatment provided protection against the DEP-induced pigmentation and inhibited the clinical pigmentary response as determined by chromametry and underlying transcriptional alterations determined by

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quantitative PCR of tape striped stratum corneum samples. The evidence that antioxidants are capable of inhibiting the actions of pollutants at the molecular scale offers a solid argument of introducing antioxidative preparations into pigment prevention protocols especially in individuals who have a high-risk factor of developing melasma, lentigines, or post-inflammatory hyperpigmentation. The application of tape stripping to the gene expression analysis in the study is a novel idea of monitoring of molecular endpoints without invasiveness with the ability of reiterating measurements in real-time without the morbidity associated with biopsy. Role of oxygen application as adjunct is another developing field of research of pigment prevention, where the Even Tone Serum study had a treatment arm in which oxygen application was evaluated following serum application. The idea behind this method is that higher levels of oxygen could increase the antioxidant activity or cellular repair, or regulate melanocyte activity via oxygen-dependent processes. Although preliminary findings indicate that oxygen adjunct therapy may have merit, such as improved pigment prevention as opposed to serum alone, the studies that have been conducted so far would require additional research to determine the optimal protocols, patient selection criteria, and mechanistic insights before such a therapy can be suggested as routine therapy in clinical practice. Combination strategies to hyperpigmentation acknowledge that already established pigmentary alterations that are the result of the establishment of pollution might need multi-modal intervention in addition to antioxidant monotherapy. Combination of the antioxidant pretreatment with the already known tyrosinase inhibitors (hydroquinone, kojic acid, tranexamic acid or azelaic acid) combats both the oxidative inducers of melanogenesis and the melanin synthetic apparatus, which could be more effective in treating patients with severe hyperpigmentation. In the case of recalcitrant pigmentary disorders the addition of energy-based devices as is detailed in the following section can be of added value, although close patient selection and order of treatment are necessary to prevent paradoxical pigment darkening or post-inflammatory hyperpigmentation(Griffiths, Watson, & Langton, 2023).

[TABLE 4: Clinically-Proven Interventions for Pollution-Induced Skin Damage]

Intervention	Active Ingredients	Study Design	Sample Size	Exposure Model	Key Outcomes	Clinical Evidence Level	Reference
CF Mix Antioxidant Serum	15% vitamin C, 1% vitamin E, 0.5% ferulic acid	Single-blind, controlled	15 females	PM + UV (4 days)	↓ 4HNE, ↓ COX-2, ↓ MMP9, preserved collagen	Level I (human controlled)	Ferrara 2024 [7]

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Even Tone Serum	Proprietary antioxidant blend	Monocenter, interventional	41 adults	DEP patch test (11 days)	Preserved ITA°, ↓ melanin index	Level I (human controlled)	Dimmers 2025 [3]
Vitamin C+E+Ferulic + QS Laser	Same CF Mix + 1064-nm Nd:YAG	Randomized split-face	18 adults	Environmental lentigines/melasma	↓ melanin index, clinical improvement	Level II (controlled trial)	Kim 2025 [8]
Broad-spectrum sunscreen + antioxidants	UV filters + antioxidant complex	Review of multiple studies	Various	Environmental exposure	Prevention of photo-pollution synergy	Level II-III	Santamaria 2025 [6]

8.5 Laser and Energy-Based Device Combinations

The evidence of antioxidants used alongside lasers is based on the fact that laser procedures produce an oxidative stress that should be avoided and cutaneous structures preserved, and therapeutic benefit should be as high as possible. Laser surgeries, especially those of pigment, induce defined thermal and mechanical damage triggering an inflammatory reaction and forming reactive oxygen species by various pathways direct photothermal lesions to cellular organization, stimulation of enzyme systems of inflammation, or discharge of pro-oxidant mediators by inflamed cells. Although inherent to the treatment mechanism of action, this oxidative stress induced by treatment presents the risk not only of adverse effects such as post-inflammatory hyperpigmentation, long-term erythema, and delayed healing. This oxidative stress can be alleviated by antioxidant pretreatment to reduce complication rates, although more aggressive treatment parameters can be used to increase the efficacy. Also, the better-skinned state obtained in the event of regular antioxidant application can contribute to the better results of laser therapy by offering healthier skin to start treatment as well as improved tissue quality and improved wound healing(Chao, Porter, & Hessler, 2023). The clinical evidence in support of using this combination therapy in pigmentary disorders is the Q-switched Nd:YAG adjuvant therapy data that a 2025 single-blinded, prospective, randomized split-face trial study offers. Eighteen lentigine and melasma patients received a vitamin C, E and ferulic acid combination antioxidant serum on one randomized side of the face immediately after receiving Q-switched Nd:YAG laser treatment and twice daily in two weeks afterward, where the opposite side was treated with laser treatment only. The spectrophotometric measurement of the melanin index showed significantly more reduction in the treated side than in the untreated one at all time points after treatment with the highest difference observed at the two weeks time(Janocha, Ziemba, Jerzak, & Jakubowska, 2024). Notably, no meaningful difference between sides in post-treatment erythema was found, which implies that clearance of pigment was enhanced without any increase in

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inflammation or risk of complications. The quantitative reduction in melanin index blindly measured by global improvement scores by the blinded investigators validated that there was greater clinical improvement on the antioxidant-treated side, which is supportive of the clinical meaningfulness of the quantitative reduction in melanin index. The enhanced results with lentigines and melasma that were seen in this study are possibly due to the combined action of various mechanisms working in different phases of the treatment and recovery process. The antioxidant formula can facilitate the crystal-induced pigment clearance, as they would maintain the activity of the melanocytes in the post-treatment remodeling period, and inhibit oxidative stress-induced melanogenesis battle related to damage. Also, the anti-inflammatory effect of the formulation could help in reducing post-procedural inflammation, which is a precursor of post-inflammatory hyperpigmentation, which is a specific issue with managing melasma. The fact that normal healing responses are maintained and adverse pigmentary sequelae are minimized indicates that the antioxidant adjuvant therapy is to a true unexplored need in the laser treatment of pigmentary disorders. Some of the practical protocols of clinical practice based on this evidence are initiation of antioxidant therapy at least two weeks before the commencement of laser procedures to optimize the skin condition and baseline protection, immediate post-procedural (after proper wound care) to address treatment-induced oxidative stress at its peak and continued twice-daily use during the healing process to aid healing and prevent recurrence of pigment(Salameh et al., 2022). The split-face study protocol, i.e., the immediate post-laser application, followed by twice-daily use in two weeks, offers an evidence-based model, which can be implemented by clinicians to their practice environments and to patients. In patients with especially recalcitrant pigmentation, the use of antioxidants beyond the 2 weeks post-therapeutic range and their combination with long-term treatments could be beneficial to the patients.

8.6 Emerging AhR-Targeted Therapies

Tapinarof and other AhR-modulating drugs have become a new therapeutic category, as they target the overall regulator of the effect of pollutants responses, with a possibility of interfering with the top of the pollution-induced cascade of damage instead of lower-level effectors. In contrast to other classes of AhR antagonists which simply block receptor activation by competitive inhibition, tapinarof is a selective activator of certain downstream pathways and inhibitor of others: this phenomenon, also known as functional selectivity, biased agonism, or ligand-directed signaling. This selective modulation allows therapeutic (anti-inflammatory effect by inhibiting IL-17 and facilitating the differentiation of regulatory T-cells) and even avoidance of adverse effects of complete AhR activation (including the possibility of CYP1 induction and the subsequent genotoxic risks). Modulation of AhR, in contrast to either simple agonism or antagonism, is a complex way of approaching this complex receptor system(Yang, Qiao, Wang, & Dang, 2025).

Potential uses in pollution protection can be based on the central role that AhR played in mediating pollutant-induced cutaneous damage as described in Section 3. Being the initial receptor of polycyclic aromatic hydrocarbons and other pollutant-produced ligands, AhR activation activates the process of CYP1 induction, oxidative stress, production of inflammatory mediators, and, finally, degradation of the matrix and the production of melanin that forms the basis of clinical effects of the pollution exposure. AhR can be pharmacologically modulated to theoretically intervene in this cascade at its very beginning and offer a better protection than the downstream interventions like antioxidants or anti-inflammatory agents that only target individual aspects of the pollutant response. Selective regulation of AhR activity, including sparing of useful functions like barrier homeostasis and immune regulation with side effects of pollutant-driven pathological signaling would provide an interesting therapeutic objective. Preclinical evidence and clinical development status This dual action is of special interest to the protection of pollution, in which the activation of Nrf2

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enhances the endogenous antioxidant response of the skin, glutathione S-transferases, NAD(P)H:quinone oxidoreductase 1, and heme oxygenase-1, which complement the action of AhR activation. The overlapping of the AhR-dependent anti-inflammatory effects and the Nrf2-dependent antioxidant benefits have theoretical benefits in terms of thorough pollution protection. Tapinarof is also approved in the United States (under the brand name VTAMA(r)) and other countries as a treatment of psoriasis with a good safety profile that has been developed in clinical studies and after-marketing use which may facilitate exploration of other indications. Nevertheless, particular clinical studies on pollution protection are yet to be published, and the off-label application of this indication would necessitate a successful selection of patients and conversation of the evidence basis. Regulatory Regulatory status and availability Regulatory status Tapinarof is approved in the United States as treatment of plaque psoriasis in adults and in children as young as 2 years old. Its application in the context of pollution protection would be considered off-label application before a certain clinical trial outcome proves its effectiveness in this indication(Rolfes et al., 2025). New AhR-regulating agents under development (both synthetic and natural product derivatives) are also possible providers of alternative as the field advances. The policy process of pollution protection claims would involve proving of clinical advantage under pertinent conditions of exposure, probably in the framework of the model of antioxidant formulation.

8.7 Natural Products with Clinical Potential

Polyphenols and flavonoids are currently the focus of numerous studies on pollution protection due to their highly-documented antioxidant and anti-inflammatory activity, their long-standing use in traditional medicine systems, and because they are perceived as natural, as opposed to synthetic substances. In a 2025 review of PeerJ, the authors summarized the mechanisms of action of natural products on PM2.5-induced skin damage, and several compounds that did have proven efficacy in preclinical models were identified, which can be used to understand how they might be used. The variety of chemical structures of natural products presents the prospects on multi-targeted methods that could tackle various consequences of pollutant-mediated damage. Natural products have been shown to exhibit preclinical efficacy at numerous mechanistic endpoints of importance to pollution protection. The sulfur-based isothiocyanate sulforaphane, which was produced by broccoli and other cruciferous vegetables, reduced oxidative stress in PM-exposed cells at the concentration of 1-5 uM by Nrf2-activation and phase 2 detoxification enzyme induction. Citrus fruits hesperidin (50 uM) inhibited the generation of reactive oxygen species and mitochondrial dysfunction of the pollutant-exposed keratinocytes. Berry and onion quercetin (25-100 ug/ml) reduced oxidative stress parameters, quantitative oxidative stress and release of inflammatory cytokine. The green tea catechins (750 ug/ml) inhibited ROS and prevented PM-induced harm in a complex of different ways such as direct radical scavenging and metal chelation. Grape resveratrol (0.1-1 uM) suppressed ROS and oxidative stress, and stimulated sirtuin pathways that mediate longevity and stress resistance(J.-K. Liu, 2022). Phlorotannin, diphlorethohydroxycarmalol (a brown algae phlorotannin, 20 uM) reduced endoplasmic reticulum stress responses and inhibited PM-induced apoptosis. Ginsenoside of ginseng (40 uM) decreased ROS, oxidative stress and inflammatory markers. This broad preclinical evidence base makes proof-of-concept in natural product efficacy but it needs to be translated into clinical environments. Difficulties in bioavailability and formulation are the major hindrances to clinical translation of natural products to protect the environment against pollution. The same review has highlighted that the low stability of natural products and their bioavailability is still an issue that needs to be considered when using them clinically, hence more research and development is needed. Most polyphenols are rapidly metabolized in the skin by phase 2 conjugation reactions (glucuronidation, sulfation, methylation) that inhibit accumulation at target sites and may result in the formation of

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metabolites with alternative biological activity. The chemical instability, especially the susceptibility to oxidation and light radiation makes them more difficult to formulate and reduces shelf life. The lipophilic or hydrophilic nature might not be the most appropriate in terms of the ideal skin penetration property, necessitating formulation approaches to improve cutaneous delivery. Nanoparticle encapsulation, liposomal formulation, chemical modification to form prodrug, and combination with penetration enhancers are all areas of active research to deal with these issues. Sulforaphane and resveratrol, among others have progressed to preliminarily clinical research on a wide range of dermatological indications, and pollution-specific research is scarce(Čižmárová, Hubková, Tomečková, & Birková, 2023). The fact that Sulforaphane can activate Nrf2 the overall master controller of the antioxidant response factors of the skin is of particular interest to pollution protection because Nrf2 activation is the means by which the cellular protective mechanisms of the skin are stimulated and not just the exogenous provision of antioxidant capacity. Topical applications of sulforaphane have been shown to protect against UV-induced erythema and inflammation, which promotes the viability of this method. The pleiotropic actions of resveratrol such as sirtuin activity, anti-inflammatory and direct antioxidant effect endorse further research on pollution protection, albeit clinical evidence is still at the preliminary stage. The way to clinical validation of natural products will have to be well controlled human studies with validated endpoints in the presence of relevant exposure conditions, as opposed to relying on historical use or in vitro data(Andrei et al., 2025).

8.8 Oral Supplementation Strategies

Systemic antioxidants as cutaneous protection agents have the theoretical benefit of delivering protective factors to a skin site through the circulation that might otherwise be inaccessible by topical application and protecting deep-cutaneous structures. The vascularity of the skin facilitates the delivery of orally administered antioxidants to the epidermal and dermal compartments but to attain adequate concentrations that will lead to clinically significant effects there is the need to take sufficient care of absorption, distribution, metabolism, and excretion. The idea of a beauty inside-out has sparked a significant consumer appeal in oral supplements to protect the skin but evidence base of pollution-specific protection is less than topical protection. Photoprotection has been studied in depth with polypodium leucotomos and other botanicals, some evidence showing that it may have beneficial effects to pollution protection as well(Morgado-Carrasco, Gil-Lianes, Jourdain, & Piquero-Casals, 2023). A tropical fern extract, Polypodium leucotomos, has been shown capable of inhibiting ultraviolet-induced damage by antioxidant and anti-inflammatory processes in numerous clinical experiments, and has been shown to reduce erythema, prevent DNA damage and immune-recovery after UV exposure. Its usage in the context of pollution protection however, has to be looked into specifically, because the oxidative stresses that the exposure to UV versus exposure to pollutants exert are different and doses used to be effective might have varying requirements. Other botanical extracts that have shown oral photoprotection such as extracts of green tea, grape seed, and pomegranate also need pollution-specific assessment in order to give advice. Carotenoids and their shortcomings explain the possibilities and the limitations of oral antioxidant methodologies to cutaneous protection b-Carotene, lycopene, lutein, and other carotenoids in the skin, as a result of oral supplementation, are an antioxidant defense, and go as far as to offer some protection against UV-induced erythema in the skin with adequate doses in the long-term. Protective concentrations in the skin however take weeks to months of regular supplementation thus limiting applicability to acute protection. Also, the lipophilic property of carotenoids restricts their diffusion to deepest areas, including the stratum corneum and sebaceous glands, which might provide only protection to the surface layers and expose the deepest layers. The carotenoid defense against pollution, in particular as opposed to UV, is poorly supported by evidence, and few studies have used the appropriate exposure models or

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endpoints. There is also a great evidence gap and the research requirement with regard to oral supplementation in protecting against pollution, which needs to be filled before the provision of evidence based recommendation can be made. Mechanistic rationale would allow potential benefit of systemic use of antioxidants-theoretically, oral antioxidants would theoretically prevent the effects of pollutant-induced oxidative stress in the whole body including the skin-however, there exists a paucity of clinical trials to evaluate the benefits of oral antioxidants to protect against pollution under real-world exposure conditions. Future research ought to use validated biomarkers of damage caused by pollutants in skin samples (tape strips, biopsies or non-invasive spectroscopy) as opposed to the use of serum antioxidant levels or survey questionnaires in general. They should balance out dietary consumptions of the antioxidants that may differ significantly among individuals and across time, which may end up confounding the outcomes. They need adequate sample sizes to identify clinically significant effects over and above personal variation. As well as they must involve objective biophysical data (transepidermal water loss, elasticity, pigmentation) and clinical examination to determine its applicability to patient outcomes(Januszewski et al., 2023). The synergistic effect of oral and topical antioxidants can have their complementary effects, yet this assumption needs to be directly tested in properly designed clinical trials.

8.9 Comprehensive Photoprotection Evolution

The shift towards protecting against UVs exclusively to broad-spectrum protection of exposome is the biggest paradigm shift in photoprotection since the development of high-SPF sunscreens in the late 20th century. The appreciation that environmental stressors other than UV e.g. visible light (high-energy visible light in the blue spectrum), infrared radiation, particulate matter of different sizes, ozone, and other gaseous pollutants and temperature extremes are also pathogenic agents of cutaneous aging has prompted the creation of multi-beneficial formulations that respond to the entire exposome (as opposed to UV). This development is an indication of better knowledge about environmental dermatology and the desire by consumers in more urbanized settings to have full protection. Physical barrier line of defense Film-forming polymers act as physical barriers in combating pollutants, which is a complementary activity to antioxidant protection by physically preventing the deposition of pollutants on the skin and into the skin. Natural biopolymers such as Tara gum (of the seeds of Caesalpinia spinosa) and red algae (such as Porphyridium cruentum) create continuous elastic films on the skin surface and minimize the amount of pollutants deposited, yet do not affect the barrier properties or cosmetic appearance(Pellacani et al., 2024). A non-invasive imaging method, reflectance confocal microscopy has been established, to provide clinical assessment of the skin surface and superficial epidermal structures at cells, and has been shown to offer extended protection during film integrity after application, up to 6 hours, to sunscreen formulations containing these biopolymers against deposition of particles by standardized procedures of particulate adhesion assays. The film forming effect also minimized transepidermal water loss and enhanced skin hydration, which countered the barrier disruption of the exposure to pollutants and offered the desired particle barrier effect. Multimetallic combination products Multiple mechanisms UV filters, antioxidants and film forming polymers are combined to offer a complete exposome protection by complementation(K. X. Tan, Chang, & Lin, 2022). The logic behind a combination strategy acknowledges that there is no one mechanism that attends to all the effects of pollutant damage: UV filters prevent photodamage caused by solar radiation, antioxidants prevent oxidative damage caused by pollutants and UV, and film-formers prevent deposition and penetration of particles on the skin. Such multifunctional formulations would have to be investigated through complex methods such as reflectance confocal microscopy to measure film integrity, colorimetry and spectrophotometry to analyze pigments, biophysical measurements (transepidermal water loss, corneometry, elastometry) to test the barrier

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and hydration performance, and standardized pollution exposure assays to test efficacy. Formulations can be screened: in vitro models of human skin can be constructed using reconstructed human skin, and mixtures of pollutants are standardized before advancement to human studies(Valenzuela, Bilicic, Hartmann, & Retamal, 2025).

Future directions The formulation science Future directions Future directions involve generation of "smart" formulations that react to environmental conditions, delivery of protection factors during an increase in pollutant concentration or release of activity in response to a particular stimulus (pH changes, oxidative stress, enzyme activity). Technologies of encapsulation that allow local delivery of antioxidants to particular parts of the cutaneous tissue such as stratum corneum to protect the skin on the surface, viable epidermis to provide protection to cells, or pilosebaceous unit to protect follicles could increase efficacy with reduced irritation and wastage. Direct-acting antioxidants which offer instant protection, plus incorporation of Nrf2 activators which upregulate the inherent antioxidant defenses of the skin, may be of synergistic value with complementary actions of action. As the knowledge about damage mechanisms caused by pollution is further developed by applying the methods of omics technologies and systems biology, the formulation strategies will also improve, providing the patients with the more sophisticated choice of options that may help them to avoid the complex of environmental attacks that modern urban life imposes on the human skin(Valenzuela et al., 2025).

9. Critical Knowledge Gaps and Future Research Directions

9.1 The Temporospatial Disconnect: Identifying the Central Gap

Pollution dermatology has achieved impressive gains in the last 10 years, but there is still a core gap in the literature that prevents us to gain full insights to the problem of skin damage caused by pollution and to treat it in all its manifestations. This temporal spatial disconnect this lack of a coherent mechanistic accounting of acute exposures to pollutants to chronic aging consequences constitutes the one and only obstacle confronting the transition of the field between descriptive epidemiology and predictive interventions which are personally determined. The existing literature discusses both the acute and the chronic effects separately in parallel but disconnected bodies of knowledge. Acute exposure studies over hours to days have revealed on a single track the elegant regulation of immediate molecular responses to pollutants; aryl hydrocarbon receptor (AhR) nuclear translocation and cytochrome P450 induction within hours of exposure; oxidative burst generation and lipid peroxidation within minutes to hours; cytokine release and inflammatory cell recruitment within hours to days; and transient regulation of barrier proteins such as filaggrin, loricrin and tight junction components over days(He, Gao, Guo, & Xie, 2024). Studies usually performed on cultured cells, ex vivo skin explants, or controlled human exposure systems, offer a detailed mechanistic understanding of the initial events that take place following pollutant exposure. In the parallel track, years to decades of epidemiological cohort studies have reported strong relations between cumulative exposure to pollution and clinical outcomes of clinical importance. An example of this is the SALIA study of German women which has shown that there are substantial links between long-term exposure to particulate matter created by traffic and wrinkle severity assessed by validated clinical scales . These findings have been validated by Asian validation studies which have shown correlations between multi-year PM2.5 exposure and the counts of lentigines, pigmentary abnormalities and the level of skin aging scores . These population level studies confirm that an exposure to pollution speeds up aging but do not give much information about how the acute molecular processes observed in short term studies are converted into long-term structural changes seen years ago(Azevedo et al., 2025). The literature on repeated acute exposures providing a mechanistic model of chronic aging does not exist. Although it is intuitively reasonable that progressive degradation of dermal architecture may occur with time as accumulation of acute

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insults (with each inducing temporary oxidative stress, inflammation and matrix remodeling) may transform reversible acute changes into irreversible chronic alterations, the exact mechanisms through which reversible acute transformations can be converted into irreversible chronic modifications are not well understood. This is not just an academic gap but has immense practical potential. When acute effects are completely reversible intermittently between exposures, then interventions can only rely on treatment of each episode of exposure. When however, the effects of acute exposures result in the development of permanent change that builds overtime, then interventions should focus on the acute injury as well as the processes of memory that translate temporary experiences to permanent change. The lack of longitudinal human evidence with intermediate outcomes is a very important evidence gap that has to be filled in order to make acute and chronic observations closer. Although epidemiological designs determine the outcomes at single time points, years after the exposure, and controlled exposure designs determine endpoints days after acute challenge, there are no studies that have followed individuals over months to years with serial measures of both pollutant exposure and intermediate biomarkers. These kinds of studies would allow tracing the pathway between acute molecular alterations and defined clinical pathology, individual differences in susceptibility and rate of progression, and define the time-frames of possibility of intervention prior to the changes taking on a permanent nature. Such longitudinal studies will require the development and validation of non-invasive or minimally invasive biomarkers that could be measured repeatedly over time as oxidized lipids, protein carbonyls, DNA damage products, and epigenetic marks in easily samable tissues such as tape-stripped stratum corneum(Burq & Verschoore, 2024).

9.2 The "Oxinflammatory Memory" Hypothesis

Hypothesis: Transient exposures to pollution cause long-term cellular alterations in epigenetic remodelling and reprogramming of metabolism. In order to fill this abovementioned temporospatial gap, we have imagined the concept of an oxinflammatory memory, which is a new concept, which assumes that the short-term exposure to pollution leads to long-term effects on the cellular changes which persist even when the exposure is stopped and accumulate over time ultimately resulting in the occurrence of the chronic aging phenomenon. This hypothesis also incorporates new evidence in several disciplines and forms predictions that can be tested to formulate future studies. Biological memory after exposure to the environment is not a new idea. The research on developmental origins of health and disease (DOHaD) has shown that early-life nutritional and environmental exposures cause permanent modifications in metabolism and disease risk by epigenetic programming. The immunological memory permits an improved reaction to secondary exposition to pathogens by creating permanent adjustments in the number and functionality of immune cells(Janjetovic & Slominski, 2024). The existence of metabolic memory after hyperglycemic episodes induces diabetic complications by causing permanent changes in their epigenetic and mitochondrial state. Through analogy, we suggest that the mechanism of cause-and-effect interrelation between acute, reversible oxidative and inflammatory events and chronic, progressive tissue damage is mediated by pollutant-induced oxinflammatory memory. It has been hypothesized that several interrelated mechanisms are the possible mediators of oxinflammatory memory that might be capable of perpetuating the effects of the pollutants long after the stimulating exposure is no longer present. Methylation in the regulatory elements of genes in oxidative stress response, inflammation and matrix metabolism may establish long-lasting changes in the expression of these genes that are retained during cell divisions(Krutmann, Schalka, Watson, Wei, & Morita, 2021). Initial indications indicate that the exposure to PM2.5 results in the activation of ten-eleven translocation (TET) enzyme and inactivation of DNA methyltransferases causing the demethylation of the p16INK4A promoter and subsequently, cellular senescence occurs to a greater extent. Histone modifications, such as the

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acetylation and methylation, or phosphorylation, may change the patterns of accessibility and gene expression that persist beyond the original stimulus. Accumulating mitochondrial DNA damage which is less repaired than nuclear DNA may result in chronic low-level production of reactive oxygen species and mitochondrial dysfunction(Sahni & Gowda, 2025).

Subsequent mitochondrial dysfunction may further maintain oxidative stress and trigger stress-responsive signaling throughput without ongoing exposure to pollution. All these possible mediators produce certain predictions to test and propose particular treatment strategies. Future research can be informed by testable predictions and experimental methods based on the oxinflammatory memory hypothesis. When the hypothesis is right, then cells or tissues subjected to pollutants would have long-lasting changes in gene expression, epigenetic marks or mitochondrial functioning once the pollutant is eliminated and the acute responses have subsided. Such changes are supposed to be linked to history of cumulative exposure and determine the aging course later. Alterations in the epigenetic marks, promoting the functionality of mitochondria, or clearing senescent cells should also alleviate the effects of pollution-induced aging when applied later in life, after the maximum exposure period(W. Zhu et al., 2025). To test these predictions, in vitro models will have to be combined with longitudinal in vivo experiments, epigenomic and metabolomic technologies will be applied, and experimental systems will be designed that will make it possible to trace a specific cell type and its progeny at a fixed time after a specific exposure conditions. There are very deep implications to intervention timing and days in case the oxinflammatory memory hypothesis is confirmed. The existing methods of pollution protection are mostly concerned with acute prevention (the application of antioxidants before or during the exposure to neutralize reactive species and prevent direct injury)(Singh et al., 2024). Although this approach is critical, the memory hypothesis indicates that interventions, which address the processes of memory persistence: epigenetic modifiers, mitochondrial therapeutics, senolytics may be of added value and especially when applied when the exposure has already been substantial. These interventions may have to be long-term or temporary in order to undo the already existing changes and not merely avoid the further damage. Whether acute protective and chronic memory-modifying interventions should be done at the optimum time, duration, and combination are some of the pertinent questions of further clinical inquiry(Rotter et al., 2024).

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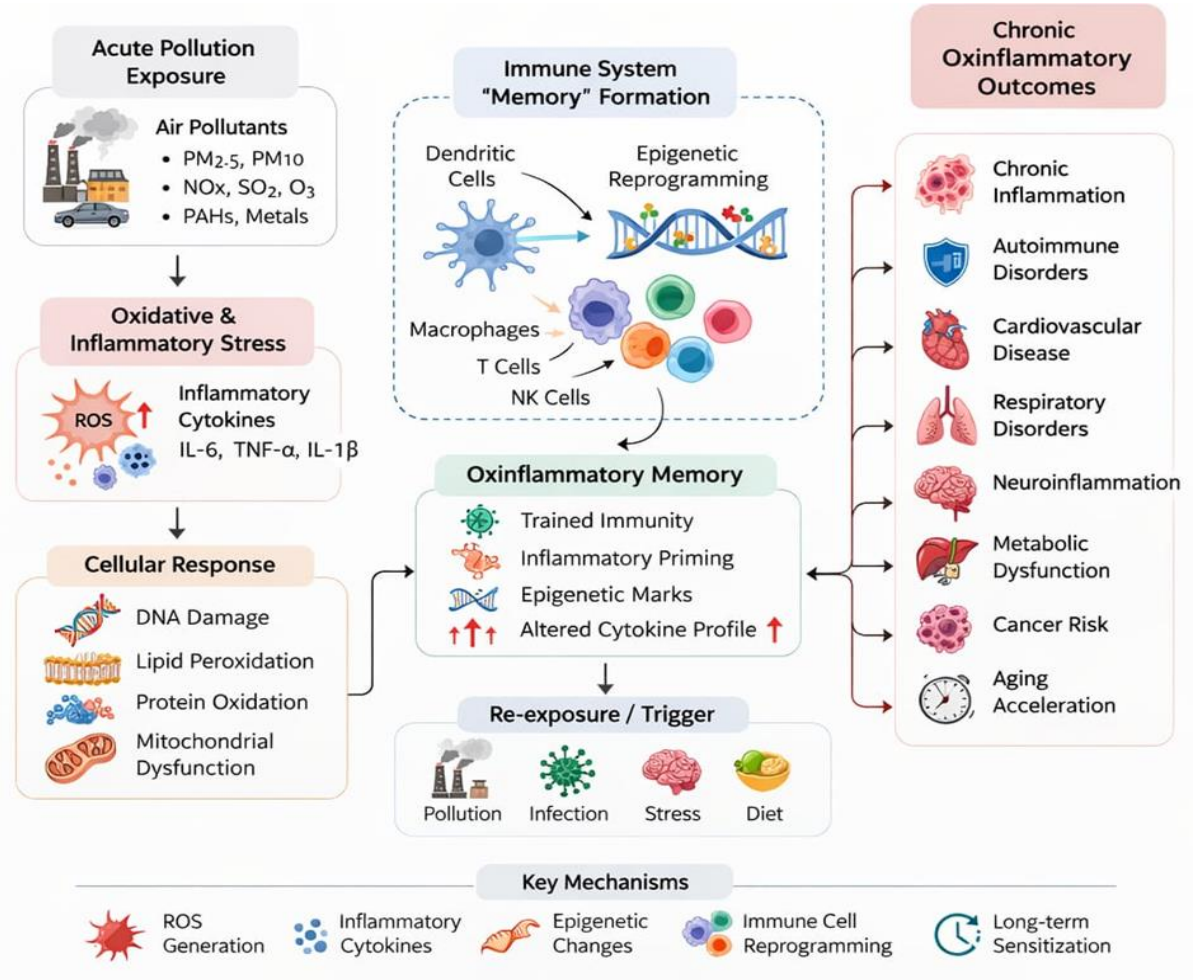


Figure 4: The "Oxinflammatory Memory" Conceptual Model

9.3 Additional Knowledge Gaps

Personal susceptibility factors are an important area of knowledge void that has personal prevention and treatment implications. Variations in the genetic polymorphic pathway of the aryl hydrocarbon receptor (AhR) such as the variants in AhR itself, ARNT (AhR nuclear translocator), and CYP1A1/1B1 can also affect the individual responses to pollutant exposure through changes in the receptor affinity, metabolic activation, or detoxification ability. The ability of the endogenous defensive mechanisms to respond to oxidative damage may be influenced by the presence of polymorphisms in antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidases, and glutathione S-transferases and predetermined vulnerability to oxidative damage(Tory, Nicole, Nina, & Richard, 2025). This method was shown to be proof-of-concept in the SALIA cohort study, which showed that the relationship between skin wrinkling and decline in lung function was only observed in the carriers of select MMP-1 and MMP-3 promoter variants, meaning that the alleles are an apparent widespread genetic vulnerability to the environmentally-induced tissue aging process. Additional research needs to assess genetic factors of pollution vulnerability in genome-wide studies, prospectively and using empirically validated study designs in well-characterized cohorts with a comprehensive assessment of exposure and a standardized outcome. Developmental etiology: early exposure in life and subsequent skin outcomes in later life are a gap in knowledge

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without potentially significant impacts on the health of the population. DOHaD paradigm has provided that prenatal and early postnatal exposures and stress factors to nutritional, chemical, and psychosocial factors set developmental lifelong health outcomes using epigenetic and developmental pathways(Gunasekara, Wang, Herath, & Sanjeewa, 2025). Whether an identical programmed skin aging trajectory with vulnerabilities being created decades later is similarly programmed through early-life exposure to pollution, is not known. This question could be answered mechanistically using animal models whose early-life exposure was controlled and then, assessed at longitudinal levels in terms of skin structure and function. To establish the relevance to human populations, human cohort studies with long-term follow-up since birth, including early-life exposure measurement and adult skin phenotyping would be necessary. Another promising field of pollution dermatology is that of microbiome-mediated effects and therapeutic targeting(J. Tan et al., 2021). The cutaneous microbiome is an example of communities of bacteria, fungi, and viruses that are vital in barrier, immune education, and pathogen defense. Exposure to pollution changes the composition of microbes and functions, but the nature of these changes, their determinants and the nature of their effects on skin health are not well defined. On the other hand, particular microbial metabolites, such as AhR ligands generated by Malassezia species could mediate cutaneous reactions to pollutants. Awareness of these two-way interactions may allow the use of microbiome-specific interventions, such as probiotics, prebiotics, or postbiotics, to improve resilience to pollution exposure. To be able to compare outcomes across investigations to develop an integrated evidence base, standardization of pollution exposure assessment in clinical studies is necessary. The existing literature uses a wide range of exposure assessment methods such as address-based exposure modeling, based on monitoring station data, personal monitoring identified by passive sampler or active pump, and in vivo exposure in a chamber. Both methods have their advantages and disadvantages and no standardized protocols are available to improve meta-analysis and synthesis of evidence(J. Tan et al., 2021). The process would speed up with development of consensus recommendations on exposure assessment in dermatological research, including minimum data elements, the preferred techniques of measurement and quality control measures. Biomarkers used in skin damage caused by pollution need to be validated so that to make use of the possibility of effective clinical trials and individual monitoring. Examples of candidate biomarkers are oxidized lipids (squalene peroxide, malondialdehyde), protein carbonyls, DNA damage products (8-oxo-dG), and inflammatory mediators (IL-1a, IL-6, PGE2) and epigenetic marks. Each must be validated against the clinically meaningful outcomes, they must be established in reference ranges in healthy population and affected population, and they must be responsive to interventions. The minimally invasive or non-invasive sampling techniques, especially the tape stripping technique to analyse stratum corneum, has the advantages of repeated measurements especially in clinical studies and practice. The importance of dose-response in various populations has not been well described though this is a crucial aspect in risk assessment and population health(Hamed, Abu Nahia, Alkilani, Al-Adhami, & Obaidat, 2024). It is probable that the connection between the concentration of pollutants, time of exposure, and the outcome on the skin depends on the age, sex, skin type, anatomical location, and genetic background. These relationships can only be characterized by studies that have detailed exposure assessment, measurement of outcomes quantitatively, and large enough sample size to identify interactions. The data obtained would provide evidence-based recommendations to sensitive populations and thresholds to be taken by regulatory action. Sooner than these new agents find their ways to pollution protection, they have to prove their long-term safety following AhR-modulating therapies. Although the approval of psoriasis using tapinarof is encouraging with respect to short-term and medium-term safety in the affected groups, there are other concerns when

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using the substance chronically to prevent pollution in healthy populations. Theoretic issues comprise a likelihood of proliferating carcinogenesis by induction of CYP1 (this is lowered by modulating agents as opposed to complete agonists), impact on immune capability, and the off-target effects. They need long-term prospective studies involving safety monitoring(Vendruscolo, Bagatin, & Leonardi, 2025).

9.4 Methodological Challenges and Solutions

The necessity to have controlled human exposure paradigms that reflect the real world scenario and allow to study the mechanistic research in a rigorously manner is the priority of the field. The current models such as the Dusseldorf Air Pollution Patch Test using diesel exhaust particles have been useful in the study of pigmentary responses, as well as assessing protective interventions. Translational relevant would be improved by extending these models to include other classes of pollutants (particulate matter, gases, semi-volatiles), durations of exposure (acute, repeated and chronic), and other stressors (pollution and UV, temperature and humidity). Exposure protocols, outcome measures, and reporting would be standardized, which would allow making a comparison across studies and meta-analysis. Relevant in vitro systems with cellular diversity to create in vitro systems that recapsulates human skin architecture are necessary to facilitate mechanistic studies and high throughput screening(Zhao, Zhen, Chen, & Zhang, 2025). Various models of human epidermis restructured with keratinocytes, melanocytes and Langerhans cells are commercially known and are growing in sophistication. Dermal-epidermal interactions can be studied using full-thickness skin equivalents that have dermal fibroblasts and extracellular matrix. Organ-on-chip systems that include microfluidic perfusion and many cell types have the promise to provide more physiologically relevant culture conditions. Combination of these systems with controlled exposure of pollutants and real-time monitoring of responses would hasten the rate of discovery and minimise the use of animals. Evidence synthesis and meta-analysis require harmonization of outcome measures of studies. Clinical (wrinkle severity scales, pigmentation index), biophysical (transepidermal water loss, elasticity, hydration), and molecular biomarker (lipid oxidation product, inflammatory mediator, matrix protein) core outcome sets of pollution-induced skin damage should be used. Consent on the basic reporting standards such as the characterization of the exposure, demographics of the participants and the statistical techniques used would improve the quality and comparability of the studies. Real-life exposure data with personal monitoring devices and smartphone-based tracking, which is incorporated in the process, allows assessing product efficacy in real-life circumstances and taking into consideration the individual difference in exposure. An example of this approach is illustrated by the recent Paris study showing correlations of individualized PM10 exposure and objective skin parameters. Such methodologies incorporated in clinical trials of protective interventions would be evidence that would be directly relevant to the everyday lives of patients(Elder, Ring, Heitmiller, Gabriel, & Saedi, 2021).

9.5 Future Therapeutic Horizons

One future form of therapeutic intervention, in case the oxinflammatory memory hypothesis is confirmed, is epigenetic modulators to undo the effects of pollution. DNA methyltransferase inhibitors (compounds that change DNA methylation), histone deacetylase inhibitors (compounds that change histone acetylation), or other epigenetic changes have the potential to reverse more lasting changes caused by exposure to pollutants. Nevertheless, the non-specificity of the existing agents, as well as the safety-related concerns such as the possibility of cancer-promoting properties, require special attention to its development and strict safety assessment before its clinical use in pollution protection(Chauhan, Singh, Singh, & Singh, 2025). Mitochondria-targeted antioxidants have the promise to relate to the chronic mitochondrial oxidative stress caused by pollutant-induced dysfunction of

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mitochondria. Mitochondrial compounds like MitoQ (ubiquinone conjugated to lipophilic triphenylphosphonium cation) and SkQ1 are taken up by membrane potential, reaching high concentrations at the location of the reactive oxygen species production(Goh et al., 2024). Preclinical models show that it is effective in mitochondrial oxidative damage models, and other indications are being investigated clinically. Pollution protection would need to be demonstrated to cause long lasting impairment of mitochondrial functions to which the mitochondrial dysfunction could be subjected. A novel approach to pollution-induced premature senescence is senolytics that in targeting the build-up of senescence cells with their senescence-associated secretory phenotype (SASP), which can promote tissue aging via paracrine action on adjoining cells. Selective senescence cell elimination drugs such as dasatinib plus quercetin (D+Q), fisetin, and navitoclax have been proven effective in increasing lifespan and minimizing pathology in old age in animal models. In case premature cellular senescence is caused by pollutant exposure, like the initial evidence indicates, then the senolytic interventions potentially may reverse the existing aging alterations despite the fact that as much damage may be caused. This hypothesis would need to be tested by clinical investigation of the pollution-exposed populations. The ultimate objective of precision dermatology is personalized prevention with the approach of susceptibility profiling. Personalized risk stratification and intervention could be made possible through evaluation of genetic predisposition (AhR pathway variants, antioxidant enzyme polymorphisms, MMP promoter variants), exposure, (personal air quality sensors, time-activity diaries), and biomarker (oxidative stress markers, epigenetic clocks) surveillance. There is a possibility that high-risk people could be recommended to implement more vigorous protection measures or be monitored more frequently or have prophylactic interventions that are not necessary commonly. To achieve this vision, a lot of investment in mechanistic research, technology development and clinical validation is needed(Dias da Rocha et al., 2024).

10. Clinical Practice Recommendations

10.1 Patient Assessment and Risk Stratification

Introduction of pollution awareness into regular dermatological practice should start with the systematic patient evaluation to determine those who are at a high risk and clinical manifestations that may be indicative of the presence of pollution in cutaneous pathology. The use of a holistic method to assess the patient allows the development of an individual practice of prevention and treatment based on the risk profile and clinical presentation(Daniele et al., 2023). History taking on the issue of pollution exposure is to be treated as the usual part of dermatological examination, especially when a patient comes with unaccounted acne flares, pigment abnormalities, or rapid aging. The clinicians are supposed to ask questions concerning the residence (urban or rural, closeness to major roadways or manufacturing sources), workplace exposures (outdoor work, transportation sector, production), commuting (duration, mode of commuting, routes), and lifestyle (how much time spent outdoors, use of active transportation, indoor air quality indicators like air purifiers). The recent innovation of smartphone apps showing personalized air quality information through GPS location allows exposure evaluation more accurately than residence based estimates in isolation. Although this technology has not yet become a regular part of clinical practice, there is future potential of personalized exposure monitoring and risk stratification with integration of such technology into clinical practice(Rocha et al., 2024). Patterns that may differentiate between damage caused by pollution and chronological or photoaging alterations are clinical signs that indicate that pollution plays a role in causing the damage. Patterns of comedones and acnes formation can give evidence of the distribution of the pollutants deposition, as the malar region, forehead, and perioral areas of the body can be involved, where the accumulation of the particulate matter is. Patterns Pigmentary changes Pigmentary changes in the cheeks, such as the

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lentigines, and in the periorbital area may have different patterns than lesions caused by pure solar. Gross wrinkle topography with related loss of elasticity, especially in those that have a history of moderate UV exposure in general, should cause suspicion of pollution contribution. Another clinical indication is given by the observation that sensitive skin, which is stinging, burning, and erythematous when the environmental stimulus is applied, is more vulnerable to the loss of barriers and inflammation caused by pollution(Rathore et al., 2024).

The special attention and intensive preventive counseling should be applied to high-risk populations. The most evident risk is increased among the urban population, and research has shown that there were significant connections between urban life and various indicators of cutaneous damage. The commuters especially those who travel by active transport (walking, cycling) or those who travel during rush hours are more exposed to the pollutants related to the traffic. Outdoor employees such as construction workers, agricultural workers, delivery workers, and street vendors do not have the same protection since they are exposed to prolonged and intensive levels. People who have pre-existing skin issues, such as atopic dermatitis, rosacea, and acne, might be prone to it because of the impaired barrier function or elevated inflammatory reactions. Recognition of such at-risk groups would allow the use of specific education and preventive measures before any clinically important harm is caused(Dias da Rocha et al., 2024).

10.2 Preventive Strategies

The most effective element of pollution prevention is the daily use of broad-spectrum photoprotection with antioxidant supplementation to overcome the UV and pollutant constituents of the environmental exposome. Sunscreens are recommended to be high SPF (30 or higher) and broad-spectrum (contain UVA1 (340-400 nm)) protection since the UVA wavelengths are known to cause PAH phototoxicity and photo-pollution synergy. Oxidative damage associated with both UV and pollutant damage can be dealt with via the incorporation of antioxidants into photoprotection regimes. An evidence base of recommending specific formulations is founded on clinical studies that have shown that the CF Mix (15% vitamin C, 1% vitamin E, 0.5% ferulic acid) inhibits the disruption of barriers by pollutants, loss of collagen, and activation of MMP. The combination of UV filters with antioxidants and film-forming polymers which physically prevent the deposition of the particles provides holistic exposome protection of the product in a single application. Balancing between effective removal of deposited particles against the risk of increasing barrier dysfunction due to excessive and aggressive cleansing is necessary to achieve gentle cleansing to remove pollutants without barrier disruption. To maximize the action on the pollutants to be removed and barrier preservation, double cleansing in oil-containing cleaner dissolving the lipophilic pollutants and mild aqueous cleanser can be used(Calderón-Pardo, Serafini, Alves, & Aragón, 2024). The cleansers must be pH-balanced (around 5.5) not to disturb the acid mantle, and include moisturizing ingredients (glycerin, ceramides) to aid the barrier activity in the cleansing process. Mechanical and chemical barrier stress is avoided by avoiding harsh surfactants, physical abrasives and hot water. Barrier repair and maintenance deals with the two-way traffic between the dysfunction of the barrier and the penetrations of the pollutants. Physiological lipids in moisturizers such as ceramides, cholesterol and free fatty acids in the right proportions maintain the structure and activity of stratum corneum. Natural moisturizing factor ingredients, such as urea, lactic acid, and pyrrolidone carboxylic acid, keep the skin hydrated and intact. Niacinamide, which enhances ceramides synthesis and decreases transepidermal water loss, provides also barrier support with anti-inflammatory effects. More rigorous repair regiments with the involvement of occlusive agents (petrolatum, shea butter) might be needed in patients with an established barrier dysfunction. Topical means of pollution protection is supplemented by lifestyle changes. Exposure is minimized by avoiding outdoor

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activities during periods of heavy traffic or heavy pollution. The purification of indoor air with the use of indoor air purifiers containing HEPA filters eliminates PMs in indoors. Physical protection such as wearing of protective clothing such as wide-brimmed hats and sunglasses serves as a barrier to the depositing of the particle. Quitting smoking and preventing second hand smoke is a way of removing a significant source of PAH exposure. Although these behavioral changes involve patient involvement, they will be of significance during the total reduction of exposure(Dias da Rocha et al., 2024).

10.3 Treatment Algorithms by Clinical Presentation

Patients with acne who are more prone to the disease in polluted environments need regimens that incorporate the traditional acnes pathophysiology, as well as the pollution contribution. Formulations with antioxidants are aimed at squalene peroxidation, oxidative stress, comedolytic, and anti-inflammatory effects. The antioxidant serum of silymarin tested in mild-to-moderate acne showed a 45 percent and 43 percent decrease in inflammatory and non-inflammatory lesions respectively, with the change in sebum production. Such formulations used together with prescription acne agents (retinoids, benzoyl peroxide, topical antibiotics) would increase efficacy with better tolerability since antioxidant serums lowered prescription-related erythema, dryness and scaling by 60, 49 and 67% respectively. Non-comedogenic barrier preparations are used to prevent the penetration of pollutants and deterioration of the follicular pathology(Mejía-Valdez, Antunes-Ricardo, Martínez-Ávila, & Guajardo-Flores, 2023). Pigmentary issues are multi-factorial and hence demand multifaceted solutions that address melanin production and its oxidative processes. Antioxidant tyrosinase inhibitors, such as vitamin C, kojic acid, azelaic acid and tranexamic acid, contain antioxidant properties that deal with melanogenesis and counteract the oxidative stress that promotes pigmentation by pollutants. The Even Tone Serum clinical trial showed that pretreatment with antioxidants inhibits the pigmentation due to the diesel exhaust and pretreatment demonstrated to prevent the pigmentation at clinical level as well as at molecular level(Daniele et al., 2023). In established hyperpigmentation, adjuvant treatment using Q-switched Nd:YAG laser, along with the application of peri-procedural antioxidants, improves the clearance of pigment and decreases the risk of post-inflammatory pigmentation hyperpigmentation . The aging issues require multi-modal intervention involving daily protection and procedural treatment of the damage that has been created. Antioxidant protection: Over-the-counter antioxidant formulations such as CF Mix have demonstrated daily that collagen degeneration will continue to be prevented and that the matrix will be maintained. Antioxidants Retinoids (tretinoin, tazarotene, adapalene) stimulate the synthesis of collagen and enhance the quality of the epidermis and complement antioxidant action. Energy-based interventions such as fractional resurfacing, radiofrequency, and microfocused ultrasound can be useful as an addition to other patients with severe wrinkles and loss of elasticity. Antioxidant support during peri-procedural as seen in the laser combination study is an associated outcome-improving intervention with fewer complications(Geng & Sibbald, 2024).

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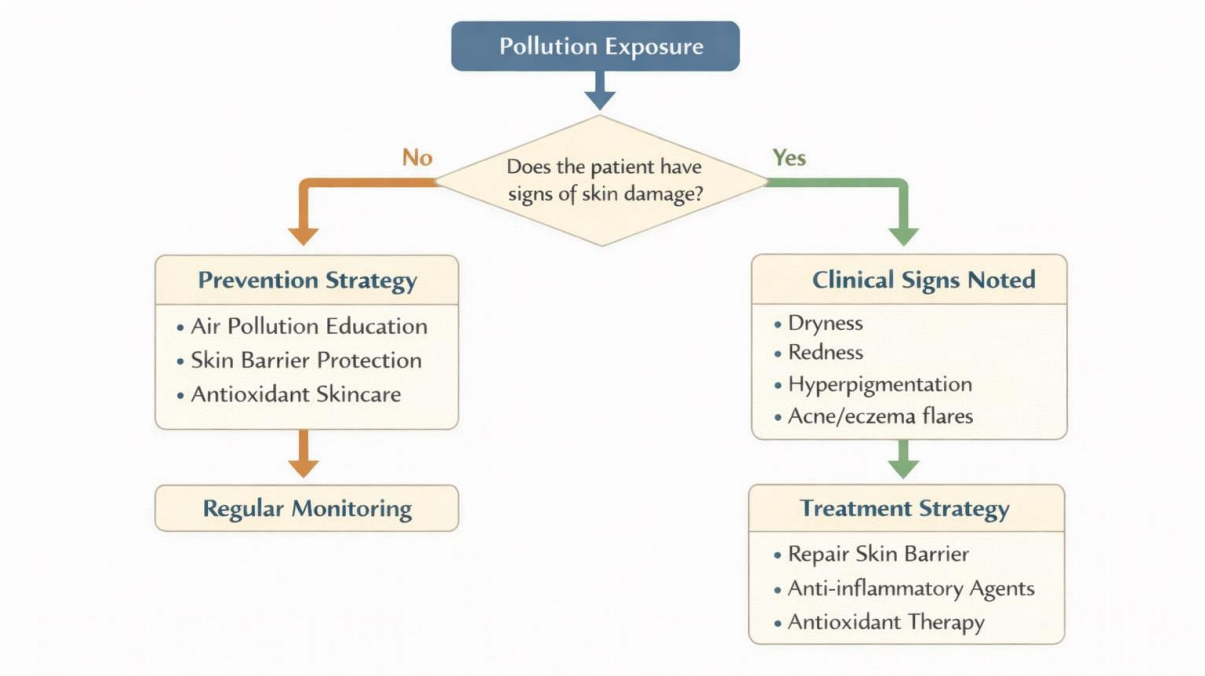


Figure 5 Clinical Algorithm for Pollution-Exposed Skin Management

10.4 Integrating New Evidence into Practice

To determine claims of products critically, dermatologists have to differentiate between marketing claims and scientifically-proven efficacy. The main aspects to be considered are the evidence base (in vitro or controlled human studies), the applicability of exposure models (single pollutant or real-life combinations), outcome measures (surrogate biomarkers or clinical outcomes), and study design (uncontrolled or randomized controlled). The products on which there are claimed to have protection against pollution should preferably show efficacy in human studies with pertinent exposure regimens and outcome measures that are validated. Evidence-based recommendation is made possible through the recognition of clinically-validated interventions(Al-Worafi, Oo, & Ramamurthy). The most well-tested intervention is the CF Mix antioxidant serum, which has undergone numerous controlled human trials showing protection against the actions of pollutants (barrier disruption, inflammation, loss of collagen and pigmentation). Another evidence-based pigment-focused concern product is the Even Tone Serum, which has evidence of preventing pigmentation due to DEP use in a clinical trial. Antioxidant serum together with Qswitched Nd:YAG laser have been found to be supported by split-face randomized trial results, which is evidence-based against established pigmentary disorders(Goodman et al., 2025). Education of the patient on pollution-skin relation provides a patient with the power to adopt protective actions and follow the suggested schedules. Elucidation of the mechanisms- how pollutants cause oxidative stress, induce inflammation and degrade collagen can facilitate the patient in understanding the logic behind prevention. The relevance of the responses to their issues is proven by demonstrating the clinical evidence of the impact of pollution on acne, pigmentation, and aging. Specific, practical, recommendations on how to protect oneself daily, what to buy, etc., and how to change their lifestyle puts scientific knowledge into everyday practical good. As the process of urbanization is ongoing, and the exposure to pollution is becoming more pervasive, the process of educating patients on environmental skin protection will become an inseparable part of the overall dermatological care(Goh et al., 2023).

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11. Conclusions

This unified molecular and clinical pathway between pollution-induced comedogenesis through to premature skin aging has been determined by the aryl hydrocarbon receptor (AhR)-reactive oxygen species (ROS)-inflammation axis that has become the central pathogenic pathway between various pollutant exposures and cutaneous pathology. We have combined evidence that air pollutants activate conserved signaling cascades the effects of which accumulate over time shifting between acute follicular pathology that expresses as comedones and acnes eruptions to chronic extracellular matrix destruction leading to wrinkles, loss of elasticity, and pigmentary changes. The molecular events presented in the review, including AhR activation, the production of oxidative stress, the activation of the inflammatory cascade, the destruction of the barrier, the damage to DNA and the inability to synthesize the matrices, can be observed throughout this clinical spectrum, which offers a single framework to understand pollution dermatology as an integrated field. We have found a significant missing link in the literature, namely there is no mechanistic model to explain the connection between the acute and reversible effects of pollutants and the chronic and progressive tissue damage and thus we have proposed the concept of oxinflammatory memory. This new paradigm assumes that temporary exposures to pollution cause long-lasting cellular changes due to epigenetic changes (DNA methylation changes, histone changes), metabolic reprogramming (mitochondrial DNA damage, sustained low-level ROS production), and cellular senescence (cells with senescence-associated secretory phenotype). The persistence of such long-lasting cycles of oxidative stress and inflammation long after the inciting exposure has stopped supports the fact that repeated episodes of acute insult can be enduring to the point of irreversibility, which causes lasting structural changes that are typical of pollution-aged skin. The oxinflammatory memory hypothesis provides new therapeutic strategies that include epigenetic modifiers, mitochondrial therapeutics, and senolytics. The field has developed considerably in clinical terms between the descriptive epidemiology and intervention-based evidence. Numerous controlled human experiments now show that dermally applied antioxidants of proper form may inhibit disruption of the barrier, inflammation, collagen degradation, and pigmentation caused by pollutants, especially that of the well-tested combination of 15 per cent vitamin C, 1 per cent vitamin E, and 0.5 per cent ferulic acid (CF Mix). The Ferrara research has determined that antioxidant pretreatment preserves epidermal barrier proteins, stops the loss of type I collagen, MMP-9 activation, and inflammasome responses after UV exposure with particulate matter. Specific pigment prevention measures such as the Even Tone Serum tested in the Dusseldorf Air Pollution Patch Test show prevention of clinical pigmentary and the expression of melanogenic genes. These combination methods involving the use of antioxidant pretreatment and Q-switched Nd:YAG laser have potential in reversing existing pigmentary damage, and randomized split-face studies have shown a significant enhancement in the reduction of melanin index in the antioxidant-treated sides. New AhR-specific interventions, such as tapinarof with its dual AhR-modulating Nrf2-activating effects, are the new category of interventions that work at the source of the pollutant response and the master regulator of it. Even with this achievement, there are still significant knowledge gaps in areas such as the individual susceptibility factors (as in MMP promoter variants results of the SALIA cohort), developmental determinants, microbiome mediating effects, and the time of intervention (given that the latter is developed). The standardized biomarkers used to describe damage caused by pollution, dose-response relationships, and long-term safety of the new therapies are the areas of interest to be pursued in the future. With the ongoing global urbanization, the concept of dermatologists no longer being involved in a treatment of well-known pathology but rather preventing the damage caused by the environment with the help of an exposome as a whole. Through her comedone-to-wrinkle framework and oxinflammatory memory concept, the author

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suggests to the researchers and clinicians the way to make a step forward in the successful prevention and evidence-based treatment of the millions of individuals exposed to the adverse effects of pollution on their skin.

THE CRITICAL GAP: "OXINFLAMMATORY MEMORY"

Why This Paper is Impactful?

The main scientific gap in this review unfilled is the temporospatial gap between the acute and chronic pollution impacts in current literature. Present studies took two parallel yet disconnected directions:

Acute intoxications (hours to days) that indicate prompt molecular actions: AhR stimulation, oxidative burst, cytokine discharge, and modification of barrier proteins.

Associations between cumulative exposure to pollution and clinical outcomes: wrinkle severity, lentigines count, and skin aging scores Epidemiological cohort studies (years to decades) describe these relationships.

The missing link is the mechanistic explanation of how acute insults repeated become permanent and progressive tissue injury. This is a gap with far-reaching consequences:

To prevent it: We do not know how the memory works, and this is why it is impossible to say what and how long we should intervene.

To treat: Injuries that have been established might necessitate varying treatment compared to injury protection.

In case of product development: Surrogate endpoints of acute protection may fail to predict benefits in the long-term.

In the case of regulatory science: There are no standardized chronic outcome measures of "anti-pollution" efficacy

The "Oxinflammatory Memory" Hypothesis

We hypothesise that short term pollution exposures have long term cellular changes due to: Epigenetic alterations DNA methylation of antioxidant response element (ARE) genes, histone modifications of inflammatory gene accessibility. Mitochondrial dysfunction: Runaway accumulation of mutations in the mitochondrial DNA, bioenergetics, and chronic low-level production of ROS. Metabolic reprogramming: Switched to glycolytic metabolism (Warburg-like effect) of cutaneous cells, distorted lipid metabolism. Cellular senescence: Senescence-associated secretory phenotype (SASP)-positive cell populations of p16/p21. Extracellular matrix remodeling: Irreversible accumulation of collagen architecture and elastic fiber integrity. This framework produces predictions that can be tested and promotes new therapeutic options that aim at knocking out the memory mechanism and not the acute effects. A review is the first attempt at fully integrating pollution dermatology, across the clinical continuum between acne and aging, both mechanistically synthesizing, and offering evidence-based therapeutic advice, as well as defining the key areas that need critical knowledge to be assessed and investigated in the next decade.

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