Deschampsia antarctica extract (Edafence®) as a powerful skin protection tool against the aging exposome

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Abstract
The impact of the interaction of all combined environmental agents to which an individual is exposed during his/her lifetime, as well as how his/her organism responds to these influences, defines health, aging, and disease. The systematic, integrative characterization of the different elements making up the "exposome" is thus necessary to identify and exploit the potential of compounds capable of conferring protection with minimal side effects. Extracts from the natural world, containing synergistic combinations of compounds with antioxidant and protective properties, have long been used in traditional medicine. Modern science has the opportunity to leverage these substances honed by evolution and use them safely and reliably, with a profound mechanistic knowledge and guaranteeing standardization and absence of toxicity. Here, we discuss our current knowledge regarding the potential of a soluble extract of the hair grass Deschampsia antarctica (as its standardized commercial preparation Edafence®) to counteract the skin exposome and its impact on skin aging and disease.
Keywords: Exposome, skin aging, skin homeostasis, detoxifying, Deschampsia antarctica, Edafence®, pollution

INTRODUCTION

Environmental agents, both natural (e.g., sunlight, moisture, and endogenous active compounds such as sweat) and derived from human activity (e.g., air pollutants, plastics, cosmetics, textiles, and tobacco), compound a sustained challenge for our organism in general, and the skin in particular, to maintain homeostasis. Our modern lifestyle and increased life expectancy demand the identification and characterization of substances simultaneously safe (i.e., non-toxic) and effective to confer protection, either directly or through boosting our endogenous defense mechanisms, including stress and DNA damage repair pathways, antioxidant and proteostatic programs, and tissue architecture remodeling. Popular wisdom through the ages has identified, basically by tinkering and intuitive experimentation, products from nature that consistently exert protection from environmental wearing of our organism. However, we have now the opportunity to, beyond practical conveniences such as safety and consistency, understand with unprecedented detail how these compounds intersect with both environmental and endogenous stressor agents, to confer protection against tissue damage.

Here, we frame our current knowledge about the activity of a soluble aqueous extract from the hair grass Deschampsia antarctica (Edafence®), a tracheophyte adapted to extreme environmental conditions and endowed with remarkable protective and antioxidant properties, on this integrative perspective and discuss underlying candidate mechanisms and therapeutic potential.

THE SKIN EXPOSOME AND SKIN HEALTH AND AGING

The basic concept that phenotype arises from the interplay between genotype and environment is most clearly portrayed by the impact external agents have on aging and disease. While environmental agents may account on their own for up to ~16% of total deaths worldwide[1], their impact on global health is far larger, as prime challenges to public health such as cardiovascular disease have a very limited (well below 50%) genetic basis[2]. At present, ~5000 toxic chemical species are identified as posing a significant threat to human population across the globe[3]. Thus, approaching the study of the impact of environment on the organism and their interplay, from a systematic and integrative perspective, is warranted. The term “exposome”, proposed in 2005 by cancer epidemiologist Christopher Wild[3], aims at capturing this dynamic, reciprocal complexity and is currently defined as the totality of exposures an organism receives from conception to death and their interplay with the organism’s response[4].

The skin is the first body barrier environmental cues encounter in our daily lives. As such, it is an organ whose physiopathology cannot be understood without considering this external influence, and the skin exposome is the central driver of skin aging and diseases such as cancer or chronic inflammatory conditions[5,6]. While classifying the wide variety of environmental agents our skin encounters is cumbersome and their interdependence or even synergy must additionally be taken into account, for simplicity, we briefly enumerate them as: (1) air pollution; (2) tobacco; (3) light radiations; and (4) other environmental agents including temperature and humidity, different chemicals from daily activities (nutrition, cosmetics, plastics), and endogenous factors such as stress and sleep deprivation [Figure 1].

Air pollution

Human activity in the industrialized era releases into the atmosphere different pollutants that, apart from inducing damage to respiratory airways and associated conditions, have a direct impact on skin homeostasis[1,3,7,8]. The list of these agents is extensive and includes ionizing molecular gas species (ozone (O₃), carbon monoxide/carbon dioxide (CO/CO₂), nitrogen species, and sulphide dioxide (SO₂)), volatile
compounds such as hydrocarbon molecules, and particulate matter, either coarse or fine (usually termed PM$_{10}$ and PM$_{2.5}$ according to their size in microns). All these compounds have been shown experimentally to induce damage and stress responses in skin cells and tissues and correlate with aging (in fact, they are precursory to a major share of differences in skin aging between urban and rural areas), but their net effect must also take into account synergistic effects among each other, as well as with radiations (see below). Their molecular action mechanism is varied, but most of these agents induce oxidative stress and damage of cell structures [for example, nitric oxide (NO) and O$_3$ can promote lipid peroxidation] and activate adaptive responses primarily aimed at reducing cell damage, which in the long term contribute to the aging phenotype [most prominently, the aryl hydrocarbon receptor (AhR), see below].

**Tobacco**

It may be considered “portable pollution”, as it constitutes an efficient means to deliver more than 2000 harmful substances to our organism and skin, including CO, formaldehyde, hydrocarbons, different toxic elements (cadmium and mercury), and tar, and, together with the characteristic effects of gestural wrinkling and skin pigmentation, its dismal impact on skin aging is well-established. Tobacco smoke induces generic oxidative stress (partly due to its impact on mitochondrial function) and DNA damage, and, importantly, it has been shown to impair activated motility and alignment of fibroblasts and wound healing. It also induces stress hallmarks of connective tissue remodeling [matrix metalloprotease 1 (MMP1)] and compromises skin barrier integrity.

**Light radiation**

Solar exposure is currently recognized as a prime environmental agent contributing to skin damage and aging, and the term photoaging has been coined to specifically describe this effect. Because of their sustained, cumulative impact throughout an individual’s lifespan and their relevance as a prime oncogenic agent, as precursor of melanomas and other skin cancers, the impact of light radiations on skin homeostasis has been intensively studied for a long time. Solar radiation, and particularly its high-energy ultraviolet radiation (UVR) spectrum, induces profuse alterations in the genomic material of skin cells, even before transformation phenotypes become apparent. These alterations are direct precursors of tumorigenesis and senescence. Light radiations are also powerful inducers of adaptive responses that can primarily counteract direct cell or tissue damage, but also intersect with pathways regulating immunity;
these links attract interest because of their potential involvement in the onset and progression of immune dysregulation, underpinning conditions such as rosacea or lupus erythematosus.

The solar spectrum comprises different wavelengths, ranging from short, high-energy wavelength radiation (UVR; < 380 nm) to low-energy infrared radiation (> 800 nm), through the visible spectrum (380-800 nm). UVR comprise ~5% of the total radiation spectrum reaching the skin but is the most energetic and is likely one of the best-studied components of the skin exposome. A major impact of short-wave ionizing radiation on skin cells is either direct DNA damage by covalent alteration of nucleic acids (mostly exerted on pyrimidine bases) or indirect damage provoked by reactive oxygen species (ROS) and other highly reactive products, derived from both generic oxidative stress and the ionizing damage of other cell structures. A relevant principle to mention is the fact that the contribution of ionizing radiations to skin damage and aging stems from a primary impact on the dermis (including the fibroblasts that serve the connective tissue and nurture other components of the dermis and the epidermal layer).

While lower energy wavelengths have long been regarded as irrelevant, several studies have demonstrated that radiation across the visible spectrum and even infrared radiations can induce significant responses in skin cells and tissues (such as pigmentation and expression of stromal remodeling enzymes for tissue repair such as MMP1), and therefore an impact on their physiology and molecular constituents. As their net load is much higher than higher-energy radiations across time, increasing attention is being devoted to their effect. Wavelengths within the visible blue spectrum are capable of inducing oxidative stress in vivo, driving significant gene expression reprogramming in skin cells and reducing keratinocyte proliferation. They may also promote a dysregulation of homeostatic molecular systems, such as those regulating osmotic balance. This specific wavelength range is currently being intensively studied because of its higher relative energy and increasing widespread exposure due to electronic devices and artificial lighting, also called digital pollution. Infrared light can exert a distinct impact on skin homeostasis and promotes specific gene expression signatures, including MMP1 upregulation; these effects may partially derive from its promotion of heat (intrinsically linked to skin aging, see below) apart from direct molecular mechanisms.

Miscellanea

Additional environmental factors, such as recurrent exposure to acute temperature changes, can promote aging, as evidenced by upregulation of different biomarkers indicating tissue damage (inflammatory infiltration, neovascularization, and oxidative DNA damage) upon exposure to heat. Indeed, severe skin aging has been observed in exposed body parts in certain occupations such as glass blowers and bakers. Dryness is also considered a hallmark of skin aging, and molecular changes such as aquaporin expression are altered with this process. It is thus not surprising that dry climates are associated with increased skin aging, commonly combining with high solar exposure and extreme temperatures.

Modern lifestyle exposes our skin to a remarkable number of agents that can have an impact on skin health. Cosmetics can deliver different damaging compounds to our skin and are thus regularly screened not only for intrinsic toxicity but, most importantly, also for their sensitizing effect in the presence of other agents such as light radiation. An additional class of external agents that can provoke skin damage are dietary components that exert metabolic stress, and byproducts of endogenous metabolism are associated with disturbed patterns of sleep and stress. Apart from major imbalances such as insulin resistance and diabetes, which are linked to systemic inflammation, high levels of certain nutrients such as carbohydrates or animal saturated fats and high-protein diets promote adverse metabolic states in otherwise “healthy” individuals and are linked to tissue aging, including skin aging. An interesting additional direct adverse effect of high carbohydrate intake on skin and other tissues has been proposed through the formation of aberrant protein-glycan adducts, whose deposition may disrupt glycoprotein structures such
as those formed by fibrillary components of the connective tissue. Additionally, these compounds may, in a similar fashion to specific pharmacological agents, sensitize skin to UV radiation.

**ENDOGENOUS MOLECULAR MECHANISMS DETERMINING THE IMPACT OF THE SKIN EXPOSOME**

A majority of environmental stressors provoke skin damage and aging through either direct disruption of cell and tissue structures, such as DNA damage by light radiation, or by fostering the accumulation of toxic molecules, such as ROS, upon perturbation of cell metabolism - most importantly, mitochondrial function. While these events can trigger proapoptotic signaling networks, such as the p53/BclX/Bcl-2 axis and the caspase activation cascade, adaptive mechanisms have evolved to counteract these aggressions to cell integrity and promote repair, as well as for efficiently and safely disposing of xenotoxins. Reflecting the intimate relationship those molecular mechanisms have with the natural process of aging, these adaptive networks are integrated with general cell stress responses and repair mechanisms, including autophagy, proteostatic Unfolded Protein Responses (UPR), inflammation, and the DNA damage response (DDR). All of these mechanisms have been found essential to counteract skin damage and aging and leveraging on them is considered a priority strategy for therapeutic intervention.

**Antioxidant and proteostatic responses**

A major aspect of cell response to exposome aggression is the deployment of adaptive responses aiming at reducing the impact of oxidative damage to cell components. Reflecting the multiple sources of oxidant molecular species, both endogenous (e.g., physiological metabolism, inflammatory states) and exogenous, several stress responses also converge on the activation of these programs, as is the case for proteostatic responses such as UPR, DDR (polyADP ribosylation, H2AX phosphorylation, and downstream networks), the ERK/p38/JNK stress signaling network, and both bulk autophagy and mitophagy. Importantly, inflammation signaling (such as the NF-κB transcriptional node) is integrated with these stress responses, feeding from and into ROS levels, and can drive tissue repair and protection as well as damage, depending on its amplitude. Evidence supports all these responses exerting protective and antiaging roles in different organisms, and in human skin in particular. In fact, natural aging is intimately associated with the decline of these mechanisms. Identifying compounds to specifically intervene in these mechanisms is therefore a priority for the prevention of skin aging exposome influence.

**AhR axis**

AhR is a conserved helix-loop-helix nuclear receptor that, upon binding with certain low molecular weight ligands, is released from quenching chaperones in the cytoplasm and orchestrates the expression of different gene subsets, primarily detoxifying and antioxidant enzymes. Both exogenous, “synthetic contaminants” and cyclic compounds generated endogenously upon exposure to UV radiation can activate AhR. Importantly, the sustained activation of this pathway itself underlies the physiopathology of the impact of different xenotoxins, and its controlled modulation is currently studied intensively for therapeutic purposes.

**Stromal remodeling and repair enzymes**

As stated above, a prime target of environmental damage and aging progression in the skin is the connective tissue servicing other structures. Indeed, a key hallmark of skin insult (which can be readily detected upon rather moderate cues such as visible light exposure) is the upregulation of certain extracellular matrix (ECM) remodeling enzymes such as matrix metalloproteases [e.g., MMP1, matrix metalloprotease 3 (MMP3)] and subsequent alterations in the architecture of ECM fibers. Other skin structural components ensuring skin barrier integrity and protection, such as loricrin, cell-cell adhesion complex components, and E-cadherin, are accordingly highly sensitive to these responses and their changes are likely to play
a relevant role in the progression of both acute and cumulative skin damage\(^5\). Finally, melanization is a specific structural adaptation of the skin to protect from ionizing radiations\(^{6,57}\). As part of skin tissue repair programs, all these architectural remodeling activities are tightly engrained with tissue damage responses and the inflammatory signaling exposed above\(^{5,15,57,65-67}\).

THE POTENTIAL OF DESCHAMPSIA ANTARCTICA SOLUBLE EXTRACT (EDAFENCE\(^\text{®}\)) TO COUNTERACT THE IMPACT OF THE SKIN EXPOSOME

As previously indicated, modern lifestyle has increased the intensity and variety of damaging environmental agents on our health, including skin. Moreover, an exponential effect may result from the combination of these different agents, as is the case for pollutant-mediated sensitization to UV radiation. As such, identifying solutions to reduce the effects of this sustained aggression is warranted\(^6\). A rich source of substances and compounds is found in the natural world, because organisms have confronted environmental damaging agents such as ionizing radiations and toxins from the beginning of time, and the molecular damage mechanisms also apply to byproducts of endogenous metabolism. Thus, compounds with antioxidant and protective activities, also capable of boosting endogenous defense mechanisms, are found in nature and have been explored for their therapeutic potential since ancient times\(^69-74\).

Deschampsia antarctica is a tracheophyte hair grass species, a polyextremophile Gramineae native to Antarctica, capable of thriving under extreme conditions of solar irradiation, temperature, dryness, salinity, and oxidative stress due to unique, evolutionary molecular mechanisms providing highly efficient protection against environmental aggression [Figure 2]. One of only two flowering plants in the Antarctic\(^75\), it partly owes its resilience to secondary metabolic routes which provide photoquenching compounds, “refolding” regulators, and dehydrins, as well as phenolic substances with strong antioxidant potential, including flavonoids such as apigenin and luteolin\(^76\). A standardized procedure for mild aqueous extraction of soluble fractions from Deschampsia antarctica has been established\(^77\), avoiding the use of organic solvents, whose associated contamination and residue carryout problems can be difficult to circumvent [Figure 2].

Briefly, dry green leaves obtained from the plant are introduced in a percolator through which water - or an aqueous solvent - is circulated under controlled temperature and time conditions. The obtained aqueous extract is then stabilized and vacuum dried. The resulting powder, Edafence\(^\text{®}\), presents activities against external aggressive factors\(^77\). Experimental and clinical evidence supports the potential of soluble extracts of this plant (Edafence\(^\text{®}\); see Figure 2) to counteract different detrimental effects of urban environment\(^78,79\).

Experimental evidence showing Edafence\(^\text{®}\) counteracting the effects of cutaneous environmental factors

Damage from air pollutants
This aqueous extract of Deschampsia antarctica counteracts damage induced by different xenotoxins and damaging agents. As a powerful oxidant commonly used as an experimental proxy of both endogenous ROS production and exogenous oxidative stress, exposure to H\(_2\)O\(_2\) induces in dermal fibroblasts senescence and DNA damage and reduces cell viability. Addition of Edafence\(^\text{®}\) was shown to powerfully counteract these effects, as assessed by the reduction of molecular stress hallmarks [sirtuin 1 (Sirt1) and thioredoxin 2 (Trx2) expression upregulation and blunting of PCNA downregulation]\(^80\). Interestingly, this extract’s protection against reduced cell viability was achieved under experimental conditions whereby the extract was added in advance to exposure to the stressor, suggesting that, in addition to intrinsic antioxidant properties, Edafence\(^\text{®}\) is effectively capable of priming protective cell states, for example through inducing endogenous antioxidant responses\(^74\). This extract also exhibits efficient protection from dioxin toxicity, as modeled by 2,3,7,8-tetrachlorodibenzo-p-dioxin; blunts AhR expression; and rescues loricrin expression
in keratinocytes. The protective effect of this extract has also been demonstrated in an in vitro system to experimentally investigate the impact of specific toxic compounds (As, Cd, and Cr) on fibroblast homeostasis.

Recent studies provide evidence indicating that these protective mechanisms also apply to conditions closer to in vivo skin physiology. Ex vivo research on human skin organ cultures (hSOC, an experimental system that preserves physiological skin architecture) suggests that this aqueous extract of Deschampsia antarctica confers protection against both toxic compound models [combining arsenic and chromium I; toxic chemical elements (TCE)] and dioxins. Indeed, addition of this extract prevented alterations to tissue architecture, skin barrier integrity (as assessed by E-cadherin expression and distribution), and dermal proliferation and significantly reduced oxidative DNA damage in hSOC exposed to TCE or dioxins [Figure 3]. These results strongly support that the mechanisms by which Edafence® protects from different sources of cellular damage, as identified through the systematic in vitro experimentation described above, are relevant in vivo.

Tobacco

This extract has been tested on other components of the skin aging exposome to determine its activity [Figure 4]. Upon exposure to tobacco smoke (5% cigarette smoke condensate extract) in vitro, this extract confers protection to human skin fibroblasts against loss of cell viability and collective organization and reverts aberrant morphological phenotypes. The effect is robust and reduces the impact of tobacco on cell viability by 66%; analogous positive results in increasing cell viability were also observed in human keratinocytes. These observations support the potential for Edafence® in counteracting skin aging through maintaining and enhancing tissue repair mechanisms, a major target for tobacco-induced skin aging.
Figure 3. Edafence® protects against xenotoxic pollutants in ex vivo experimental models of skin integrity. Human Skin Organ Culture (hSOC) belongs to human skin biopsy samples from aesthetic surgeries. It was chosen as an experimental model to investigate the potential protective effects of this extract against exemplary chemical contaminants, including Toxic Chemical Elements (TCE: As and Cr) and dioxins. A: micrographs of H-E stained sections from hSOCs treated as indicated. Note severe morphological alterations induced by prolonged exposure (seven days) to common air pollutants, including Toxic Chemical Elements (TCE: 9 mmol/L As + 0.5 mmol/L Cr) and dioxins (10 nmol/L 2,3,7,8-tetrachlorodibenzen-p-dioxin). Note apparent subepidermal blister (SEB, arrows) in TCE-treated cells; exposure to dioxin also causes significant disorganization of epidermal layers (arrows). These alterations, indicative of a critical loss of skin function, are effectively prevented by Edafence® (2.5 mg/mL). Bars: 50 µm; B: immunofluorescent staining of sections of hSOCs treated as indicated. Immunolocalization of the epithelial cell-cell adhesion molecule E-cadherin (ECCD1) confirms the extensive structural alterations of suprabasal epidermal layers induced by TCE/dioxin exposure and the protective effect against them conferred by the aqueous extract of Deschampsia antarctica treatment. Bars: 50 µm. Adapted from [82].

Figure 4. Edafence’s protective effects in vitro against other exposome agents. A, B: Edafence® incubation protects from damage induced by tobacco in human dermal fibroblasts (HDFs). It reduces loss of cell viability associated with exposure to tobacco smoke [(A) CSC: 5%, 3.5 h; Edafence® incubation: 10 mg/mL]. It also prevents alterations in collective organization (i.e., alignment) and morphological phenotype (B) compare (1) control CSC-exposed to (2) CSC-exposed supplemented with the extract). Scale bar: 100 µmol/L; C, D: Edafence® incubation protects human keratinocytes from both acute cold shock (data on the left, blue spotted pattern) and heat exposure (data on the right, blue background pattern). Primary human keratinocytes were subjected to the indicated treatments. Subsequently, cell viability was measured through crystal violet staining extension (C) and mitochondrial integrity/function was assessed by measuring mitochondrial potential with MitoTracker™ staining (D). *P < 0.05; **P < 0.01. Adapted from [77,83]. CSC: cigarette smoke condensate.
Light radiations

Protection of skin cell types (mostly keratinocytes and skin fibroblasts) against the effects of solar radiations by this extract of Deschampsia antarctica has been explored in detail. Exposure to this extract protects human dermal fibroblasts from deleterious effects induced by high-energy UV radiation, including senescent visual phenotypes, oxidative DNA damage (as assessed by DDR hallmarks: poly-ADP ribose polymerase cleavage and H2AX induction), proapoptotic stress signaling (p38/JNK activation, caspase-3 cleavage, and increased autophagy flux), and expression of ECM remodeling enzymes (MMP1) \[81\].

Importantly, recent studies support that Edafence® also counteracts the damaging impact exerted by radiation within visible and infrared spectra on both human fibroblasts and keratinocytes \[84\]. Incubation with this extract reduces the accumulation of oxidative DNA damage-associated H2AX and the activation of autophagy and caspase signaling associated with visible light/infrared radiation (VL/IR) exposure [Figure 5]. Accordingly, exposure to Edafence® reverted reduced cell proliferation and the altered expression of ECM constituents (cathepsin K, MMP1, collagen I, and elastin) in a dose-dependent manner.

As aforementioned, an increasingly studied agent challenging skin homeostasis in modern life is high-energy blue light, a radiation wavelength emitted by digital devices and therefore reaching our body for extensive periods of time. Recent studies \[85\] mimicking artificial blue light exposure on in vitro cell cultures revealed that these wavelengths reduce cell viability (an effect more pronounced in melanocytes than in dermal fibroblasts), promote hyperpigmentation and morphological alterations, and induce mitochondrial dysfunction and oxidative stress. Of note, addition of Edafence® counteracted these effects and reduced oxidative stress and ROS accumulation, mitochondrial homeostasis, and stress markers in fibroblasts, as well as melanization of keratinocytes \[85\].

The molecular mechanisms at play remain to be fully understood, but both the intrinsic antioxidant activities of this extract bearing species capable of directly quenching oxidizing radicals as well as its ability to boost homeostatic programs in the cell, including endogenous antioxidant responses \[78\], could underpin the protective action of Edafence® against different sources of damaging light radiation.
Miscellanea

The studies described above suggest that the protective properties of this extract apply to a wide range of environmental agents driving cell and tissue aging. In fact, unpublished research\[^8^6\] supports that this compound may attenuate “natural” aging and replicative exhaustion, as its supplementation reduces time-dependent telomere shortening in an in vitro human keratinocyte system [Figure 6] and positively regulates stem cell proliferation and DNA damage repair. Cellular DNA damage drives keratinocytes into terminal differentiation\[^8^7,8^8\]. The aqueous extract of Deschampsia antarctica enhanced the potential of cellular repair and as a result protected the capacity of epidermal stem cells for self-renewal, supporting its positive effect on replication and differentiation potential\[^8^6\]. These observations are particularly interesting as they might suggest that a protective mechanism for this extract relies on a positive impact on tissue repair and regeneration.

Temperature is another challenge against which Edafence\[^\textregistered\] has been shown to confer significant protection under controlled experimental conditions [Figure 4]. Exposure to this extract protected human keratinocytes from both severe cold shock and heat, as assessed by measurements of cell viability and mitochondrial function (i.e., mitochondrial potential)\[^7^7\]. The relative extent of this protective effect is higher in harsher conditions (i.e., during extended periods of heat shock; 60 min vs. 45 min at 42 °C), suggesting that protection conferred by this extract is sustained through time and is independent from

Figure 6. Edafence\[^\textregistered\] attenuates natural aging in human primary keratinocytes as assessed by telomeric length. Primary human keratinocytes were subject to in vitro aging (24 days) under indicated conditions with and without Edafence\[^\textregistered\] treatment, 0.9 mg/mL, and processed for in situ hybridization (fluorescence in situ hybridization (FISH)) with a fluorescent probe targeting telomeric repeats (Telom. FISH, red signal; 4,6-diamidino-2-phenylindole counterstain, blue signal). Telomeric signal, as a proxy of telomere integrity/length, was acquired on a fluorescence microscope and computed as indicated. Scale bar: 10 \(\mu\)m. ** \(P < 0.01\). Adapted from\[^8^6\].
the specific nature of the external challenge applied. Similarly, exposure to Edafence® confers protection in keratinocytes and fibroblasts to moderate dehydration and hyperosmotic shock, improving viability in a dose-dependent manner. These results suggest a genuine capability of Edafence® to counteract damaging stimuli, which likely extends to most elements in the skin aging exposome. Again, these *in vitro* studies further support the notion that Edafence-induced protection is durable (i.e., its effects continue after the exposure to the aqueous extract of *Deschampsia antarctica* and are comparatively higher upon longer exposure to damaging agents) and likely operates through integrated mechanisms, effective in the face of aggressions of different nature.

**Clinical studies on Edafence®**

Bearing in mind the importance of correlating the *in vitro* and *ex vivo* findings with the potential *in vivo* relevance of these compounds, studies were conducted on the effect of topical preparations containing this extract on different parameters indicative of skin health and aging.

A first set of studies explored the potential impact of this extract on skin aging under conditions of relatively high air pollution (metropolitan Rome at different times of the year). Milani *et al.* reported improvement of skin barrier function (as inferred by transepidermal water loss measurements), reduction of squalene peroxidation ratios, and enhanced visual appearance as assessed by high-resolution digital imaging. Of note, these studies covered conditions of both high particulate air pollution (winter season) and elevated O3 levels (summer season).

An additional recent study examined the impact of topical administration of Edafence-containing preparations on features indicative of general skin aging, among a homogeneous population (female, Caucasian with Fitzpatrick’s Skin Types III and IV, aged 45-65 years). Quantitative measurement of features such as wrinkling (transient reduction ranging 20%-30% after four-week treatment, as evaluated quantitatively using digital imaging), firmness, and elasticity (up to 41.7% and 12.8% improvement, respectively, after 12-week treatment) indicated a positive effect of this extract on skin health and even moderate repair of aged skin, together with remarkable subjective improvement reported by tested subjects (100% of subjects stated significant improvement in skin texture and brightness) and tolerance of the relatively high-dose preparations. This preliminary research encourages larger studies investigating the potential synergy with concomitant interventions such as nutraceuticals, moisturizing creams, and sunscreen preparations. Taken together, these studies support that the aqueous extract of *Deschampsia antarctica*, in combination with antioxidants and retinoids (products formulated by Cantabria Labs), bears potent anti-aging activity through the improvement of skin barrier integrity and function, normalizing skin tone and counteracting oxidative stress in polluted urban zones. These observations are in agreement with the aforementioned body of *in vitro* and *ex vivo* research outlining the biological basis of the protective potential of Edafence® against external aggressive factors.

**CONCLUSION**

The critical impact exerted by environmental factors on skin and organism health is best understood within the integrated framework provided by the exposome concept. Accordingly, our search for preventive and/or therapeutic antiaging and antixenotic solutions should ideally aim for products conferring protection against a wide array of damaging agents. Edafence® may fit this objective: it confers protection against environmental stressors in urban areas and prevents different clinical signs of skin aging (e.g., dehydration, wrinkles, hyperpigmentation). Different experimental models, including advanced systems approximating *in vivo* skin architecture and complexity, support its activity on counteracting cell and tissue damage from different stressors such as ionizing radiation, toxic compounds, tobacco, or natural aging. On the basis of the observations outlined here, future studies will shed light on the mechanistic basis of its...
activity and, most importantly, on the translation of those promising in vitro and ex vivo findings to the effects attainable in vivo.

DECLARATIONS

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Authors’ contributions

Substantially contributed to the conception and design of the review: Pérez-Davó A

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Availability of data and materials
All unpublished data sources have been listed here or registered under European Patent Office number (EP 3471 835 B1). Further details and materials will be fully provided upon request to corresponding authors. Any print permits from copyrighted material as been confirmed.

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Conflicts of interest
Rodríguez-Luna A, Milani M and Pérez-Davó A are members of the Innovation and Development Department, the Medical Department of Cantabria Labs Difa Cooper, and the Medical Affairs Department, respectively, at Cantabria Labs. The remaining authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
All authors provided approval for publication of all content, contributed to manuscript revision, and read and approved the submitted version.

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REFERENCES
42. Gill V, Kumar V, Singh K, Kumar A, Kim JJ. Advanced glycation end products (AGEs) may be a striking link between modern diet and health. *Biomolecules* 2019;9:888.


58. Mataix J. IFC- P1403C: Efecto de EDAFENCE® sobre el daño al DNA, muerte celular, sufrimiento mitocondrial, MMP-1 y expresión.

59. Juarranz Á. IFC- P1403C: Efecto de EDAFENCE® sobre el daño al DNA, muerte celular, sufrimiento mitocondrial, MMP-1 y expresión.


66. Linhén J, Lenou S, Tuomisto J, Pohjaniitty R. Dioxins, the aryl hydrocarbon receptor and the central regulation of energy balance. Front Neuroendocrinol 2010;31:452-78.


de proteínas de diferenciación y adhesión en fibroblastos y queratinocitos humanos expuestos a UVB, UVA, IR y VIS. Industrial report. Spain: Universidad Autónoma de Madrid; 2017.


90. Milani M, Piacentini M, Celleno L. A serum containing deschampsia antartica extract, ferulic acid and vitamin c has anti-pollutant effects on skin exposed to high tropospheric ozone levels: a controlled single-blind, prospective clinical trial in women living in urbanized, high air pollution area during the summer season. *J Clin Exp Dermatol Res* 2019;10:510.