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Skin ageing and topical rejuvenation strategies

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Abstract

Skin ageing is a complex process involving the additive effects of skin's interaction with its external environment, predominantly chronic sun exposure, upon a background of time-dependent intrinsic ageing. Skin health and beauty is considered one of the principal factors perceived to represent overall 'health and wellbeing'; thus, the demand for skin rejuvenation strategies has rapidly increased, with a worldwide annual expenditure expected to grow from $US24.6 billion to around $US44.5 billion by 2030 (https://www.databridgemarketresearch.com/reports/global-facial-rejuvenation-market). Skin rejuvenation can be achieved in several ways, ranging from laser and device-based treatments to chemical peels and injectables; however, topical skin care regimes are a mainstay treatment for ageing skin and all patients seeking skin rejuvenation can benefit from this relatively low-risk intervention. While the most efficacious topical rejuvenation treatment is application of tretinoin (all-*trans* retinoic acid) – a prescription-only medicine considered to be the clinical 'gold standard' – a hybrid category of 'cosmeceutical' products at the midpoint of the spectrum of cosmetics and pharmaceutical has emerged. This article reviews the clinical manifestations of skin ageing and the available topical treatments for skin rejuvenation, including retinoids, peptides and antioxidants.

Intrinsic skin ageing

Chronological or intrinsic skin ageing occurs with the passage of time. Clinically, the skin appears dry and atrophic, with fine wrinkling.[1] Functional changes occur as a result of impaired lipid synthesis, with a subsequent increase in transepidermal water loss and dehydration. The dermoepidermal junction flattens and the dermis becomes atrophic.[2] The overall result is reduced barrier function and increased skin fragility.[3,4] However, environmental or external factors are recognized to have a greater effect on skin appearance and are therefore suitable targets for 'antiageing' therapies.

Extrinsic skin ageing

Ultraviolet radiation (UVR) from the sun is well recognized as the primary environmental factor responsible for extrinsic ageing, known as photoageing.[5] Short-wave ultraviolet B (UVB) rays primarily impact the epidermis with excitation of reactive oxygen species (ROS) and subsequent cytokine cascades, leading to the upregulation of intranuclear transcription factor activator protein 1 (AP-1). This results in the production of matrix metalloproteinases (MMPs), which break down dermal collagen and other proteins in the extracellular matrix (ECM). Ultraviolet A has a longer wavelength than UVB, allowing deeper dermal penetration and resulting in a direct impact on fibroblasts and the activation of AP-1. This not only stimulates the production of MMPs, but also has a negative impact on the formation of procollagen.[6] A vicious cycle ensues with impaired repair of damaged ECM proteins coupled with reduced synthesis of healthy collagen. There is increasing evidence that longer wavelengths of the electromagnetic spectrum, including infrared and visible light (particularly blue light), also play a role in photodamage and photoageing. Skin irradiated with infrared and visible light has significantly increased MMP expression and decreased type I procollagen expression, implicating both in the degradation of dermal collagen.[7] Furthermore, visible light can independently generate ROS, proinflammatory cytokines and the expression of MMP-1,[8] and has been shown to play a role in angiogenesis and melanin dyspigmentation.[9]

The clinical impact of photoageing varies; two distinct phenotypes have been identified: hypertrophic and atrophic. Sallowness, skin laxity, deep coarse wrinkling and solar elastosis are hallmarks of the hypertrophic variant.[5] In contrast, the atrophic phenotype is associated with smooth, shiny, 'plump' appearing skin, along with redness and telangiectasia (Figure 1). Importantly, the atrophic phenotype has also been shown to have an increased predisposition to keratinocyte cancers vs. those with the hypertrophic phenotype,[10–13] although the key changes that produce an oncogenic environment have yet to be elucidated. Variation in the features also exist based on ethnicity or ancestral origin. Dyspigmentation appears to be the predominant trait in East Asians vs. that of wrinkling in those with European ancestry.[14,15]

Tobacco smoking is also recognized as an independent risk factor for accelerated skin ageing,[16,17] with a dose–response relationship between pack-years of smoking and wrinkling, although the impact on dyspigmentation in the form of lentigines is less clear. Air pollution is recognized to play a role

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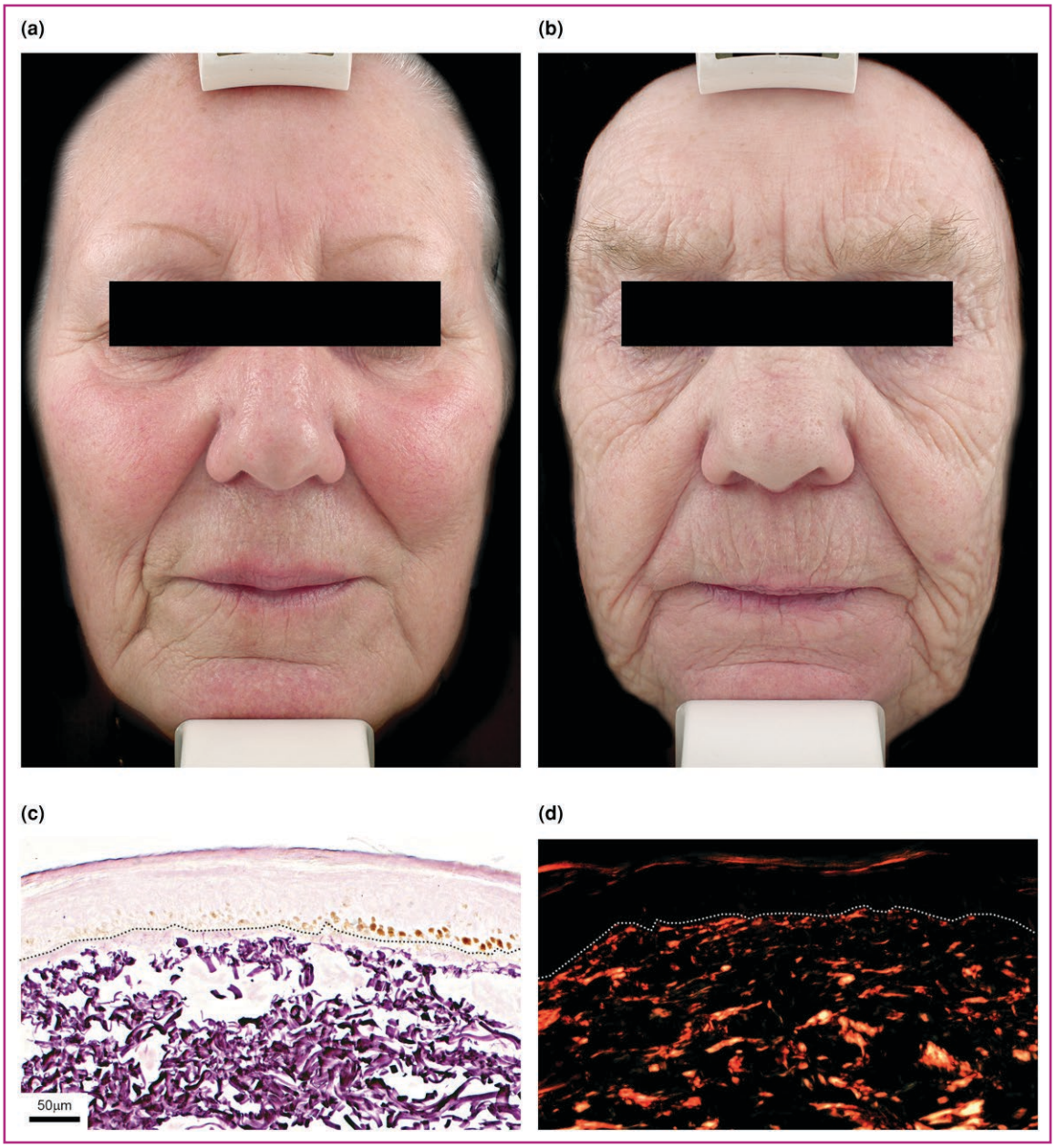

Figure 1 Clinical photographs of (a) atrophic photoageing and (b) hypertrophic photoageing. (c) Weigert's resorcin fuchsin staining identifies severe amorphous elastin or 'solar elastosis' within the dermis of photoaged facial skin. (d) Picrosirius red staining identifies loss of organized fibrillar collagens within the dermis of photoaged facial skin. Scale bar = 50 μm; dotted line = dermoepidermal junction.

in extrinsic skin ageing, manifesting both as dyspigmentation (lentigines) and wrinkles.[18] Fossil fuels, nitrogen dioxide, particulate matter, traffic-associated particles and second-hand tobacco smoke have all been implicated. Concomitant UVR with air pollution exposure further accelerates damage.[19] Nutrition and diet studies examining the impact on skin ageing are heterogenous, investigating a diverse range of food groups and micronutrients. Despite this, it is clear a healthier diet appears to be associated with less severe skin ageing; increased vegetable consumption is significantly associated with decreased wrinkling, although no significant associations have been made with alcohol consumption.[19] Other external factors include the negative impact of stress on skin ageing,[20] as well as sleep deprivation.[21]

Retinoids

Among the variety of topical skin rejuvenation treatments, retinoids are the most commonly used active ingredients, as there is sound clinical evidence that they induce skin repair. The retinoid family comprises vitamin A (retinol) and its natural derivatives such as retinoic acid, retinaldehyde and retinyl esters, as well as many synthetic derivatives. Tretinoin (all-*trans* retinoic acid) is not only approved as a prescription medicine for the treatment of acne vulgaris, but is also the clinical 'gold standard' for skin rejuvenation, as there is robust clinical evidence that its use reduces fine and coarse wrinkling and hyperpigmentation, and improves skin texture.[22–26] Hence, it remains the most

potent and best-studied retinoid. Numerous clinical studies have confirmed the efficacy of tretinoin in the treatment of photoaged skin at concentrations ranging from 0.01% to 0.1%; the most commonly used are 0.025%, 0.05% and 0.1%.[25,27–34] In the epidermis, tretinoin treatment stimulates basal keratinocytes to proliferate, resulting in epidermal hyperplasia,[25,34–37] while the stratum corneum initially compacts in response to treatment (potentially improving the interaction of light with the skin's surface); however, over time it returns to a normal honeycombed morphology.[28] In addition to epidermal changes, remodelling of the dermal ECM occurs. Tretinoin effectively reverses the deleterious intrinsic and extrinsic effects of ageing on collagen homeostasis by realigning the balance between collagen synthesis and degradation;[38] fibroblasts are activated by tretinoin to synthesize new collagen;[35,36,38,39] concomitantly, MMP activity is reduced, while tissue inhibitors of MMPs (TIMPS) are increased.[40–42] Furthermore, the application of tretinoin has been shown to induce the *de novo* synthesis and deposition of the papillary dermal fibrillin-rich microfibril network[43] – a process thought to be driven by the activation of basal keratinocytes.[44,45] Although tretinoin is the most efficacious treatment option, its use is often associated with the occurrence of erythema, pruritus, stinging, burning and scaling.[29,37,46] This local irritation induces changes to the expression of cornified envelope proteins (e.g. loricrin and small proline-rich proteins), loss of corneocyte cohesion, hyperproliferation of the basal keratinocytes and accelerated desquamation,[47–50] mediated, in part, by its impact on the expression of desmosomal proteins.[51] These physiological changes alter the functional integrity of the epidermal barrier resulting in increased transepidermal water loss.[27,52–54] However, retinoid dermatitis is often short-lived, although some reports of intermittent irritancy has been associated with continued use,[28] and the integrity of the skin's barrier eventually improves, with the use of emollients helping to counter irritancy problems.[55,56] Interestingly, it is postulated that it is the skin irritancy associated with tretinoin use that drives the active remodelling of the dermal ECM and ultimately leads to the improvement of the clinical features of photodamaged skin.[47,57]

These early studies demonstrating the efficacy of tretinoin for topical skin rejuvenation were pioneering and have given rise to the widespread inclusion of other cosmeceutical retinoid compounds in today's skincare products. Retinol, retinaldehyde and retinyl esters are not classed as drugs and therefore are widely used in cosmeceutical products, in part due to their stability in formulation.[58] Retinol is also better tolerated than tretinoin,[35,59] although local irritation, including mild erythema and peeling can still occur.[60] Cosmeceutical products containing retinol and retinyl esters are widely available over the counter and have been reported to have comparable efficacy to tretinoin.[61,62] In 2022, Chien *et al.* reported that a topical formulation containing a combination of three retinoids (retinol 1%, retinyl acetate 0.05% and retinyl palmitate 0.05%) was comparable in terms of antiageing efficacy to a topical tretinoin 0.02% formulation.[63] However, because retinoids present as active ingredients in cosmeceuticals must be converted to tretinoin after application, some researchers have questioned whether their efficacy is comparable to tretinoin.[64–66] Despite these differences in opinion, there is evidence that many of the clinical and biological effects of retinol on the skin mirror those of tretinoin, including improvement of skin texture, rhytids and dyschromia; regulation of keratinocyte growth and differentiation; epidermal hyperplasia; compaction of the stratum corneum; collagen synthesis; reduced MMP activity; and the deposition of fibrillin-rich microfibrils.[35,40,55,67–69]

Peptides

Peptides first entered the cosmeceutical field in 1973 when Pickart *et al.* proposed the synthetic peptide glycine–histidine–lysine tripeptide (GHK) as a signal peptide that could both enhance collagen production and act as a carrier peptide when complexed with copper.[70] Later, it was determined that the same tripeptide might be liberated by proteases at the site of a wound and exert *in situ* healing effects by acting as a natural feedback signal to fibroblasts to stimulate the neosynthesis of ECM proteins.[71] Thanks to their versatility, a plethora of small peptides of cosmeceutical interest has since been developed to boost ECM protein synthesis and turnover in skin, thus restoring – at least in part – damaged ECM.[72,73] Many of these peptides are thought to act as 'matrikines', a concept that peptide fragments produced naturally during ECM protein processing – most commonly from collagen or elastin – can act as signalling intermediates, stimulating cells to increase ECM production.[74] One of the most common matrikines found in topical skincare products today is palmitoylated lysine–threonine–threonine–lysine–serine (KTTKS), which is marketed under the proprietary name Matrixyl® (Sederma, Le Perray-en-Yvelines, France). Matrixyl is the signal peptide fragment of the C-terminal propeptide of type I collagen and has been shown to stimulate feedback regulation of new collagen synthesis and ECM proteins,[75] while conjugation with the palmitoyl moiety ensures its effective delivery across the skin barrier.[76] Matrixyl is well tolerated by the skin and was found in a double-blind placebo-controlled split-face trial to cause a visible improvement to fine lines and wrinkles by both quantitative technical and expert grader analysis.[77] It is also customary to find proprietary formulations containing combinations of matrikines with additional cosmeceutical products.[78] For example, Matrixyl and palmitoyl tetrapeptide-7, in combination with natural extracts of white lupin, ginseng and mulberry, was found in a double-blind randomized clinical trial to provide significant clinical improvement to facial wrinkles, which was associated with significant histological deposition of fibrillin-rich microfibrils within the papillary dermis.[79] Furthermore, this study demonstrated that an over-the-counter cosmetic product could produce significant improvement in the appearance of wrinkles and dermal repair akin to that observed using retinoids.[79]

The novel bioactive tetrapeptide GEKG (glycine–glutamic acid–lysine–glycine) has also been identified in several ECM proteins and is thought to be capable of inducing wide-ranging ECM deposition through matrikine signalling.[80] When tested topically on 10 healthy volunteers in a double-blind placebo-controlled randomized trial, daily application over 8 weeks led to increased levels of collagen I mRNA and increased formation of procollagen I, hyaluronic acid and fibronectin.[80] In addition, significant improvements to resilient distension, wrinkle appearance and skin roughness

have also been reported.[80] More recently, the conjugation of vitamin C with GEKG was shown to increase the expression of basement membrane proteins, resulting in a synergistic antiageing effect.[81] Uneven skin pigmentation is also a significant cosmetic concern in photoaged skin, and the identification of tetrapeptide proline–lysine–glutamic acid–lysine (PKEK) as a modulator of skin pigmentation has led to it being used in many topical cosmetic formulations. This tetrapeptide is reported to reduce pigmentation by decreasing interleukin (IL)-6 and IL-8, α-melanocyte-stimulating hormone and tumour necrosis factor-α expression in *in vitro* and double-blind clinical studies.[82] Palmitoyl tripeptide-5 is a patented peptide with the brand name Syn®-Coll (DSM, Basel, Switzerland); it acts by stimulating the transforming growth factor-β, inducing collagen biosynthesis and inhibiting MMP degradation of collagen. However, when conjugated with ascorbic acid (palmitoyl–KVK–L-ascorbic acid) it has proven in clinical trials to be an effective antiageing agent that reduces both wrinkles and abnormal skin pigmentation.[83]

In addition to signal peptides, neurotransmitter inhibitor peptides have been synthesized to mimic the effects of botulinum neurotoxins. One of the best-known peptides with neurotransmitter-inhibiting properties is the synthetic hexapeptide, acetyl hexapeptide-3 or Argireline® (Lipotec, Barcelona, Spain). It has shown promising clinical results in reducing wrinkle depth when applied topically at a 10% concentration,[84–86] and has been reported to induce collagen synthesis in mouse models.[87] Pentapeptide-18, or Leuphasyl® (Lipotec), is another popular active peptide with neurotransmitter-inhibiting properties used in antiageing formulations. It has been shown to be effective in wrinkle reduction,[88] and the addition of D-tyrosine to its terminus endows the peptide with the ability to reduce the melanin content and tyrosinase activity in primary melanocytes.[89] However, in comparison to botulinum toxin, both Argireline and Leuphasyl present lower efficacy but are considered as safe, nontoxic alternatives for botulinum family compounds.

Antioxidants

Antioxidants play an important role in preventing or slowing the process of cutaneous ageing, and while the consumption of antioxidants in food and supplements can be of benefit, there is growing evidence that topical use of antioxidants has clinical benefit. Many topical rejuvenation formulations contain vitamins and vitamin derivatives that perform both protective and reparative functions. Vitamin B3 is an umbrella term denoting several related molecules, including nicotinic acid (niacin) and niacinamide. These molecules are important components of the enzymes nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, which play critical roles in mitochondrial oxidative phosphorylation.[90] It has long been established that niacinamide exerts an anti-inflammatory effect, demonstrated by the efficacy of topical niacinamide in the treatment of inflammatory acne vulgaris.[91] More recently, niacinamide has been shown to mitigate the skin's inflammatory response elicited by exposure to environmental stressors, such as UVR and pollution, by inhibiting cellular senescence and maintaining epidermal homeostasis.[92–94] Clinically, topical niacinamide is extremely well tolerated by facial skin and provides several beneficial effects for ageing skin, such as improved barrier function, and decreased appearance of signs of facial photoageing such as texture, pore size, hyperpigmented spots, red blotchiness, sallowness and reduced sebum production.[95–99] Although the facial rejuvenating effects of niacinamide are similar to those reported for tretinoin, topical tretinoin 0.025% continues to be a more potent technology with niacinamide reported to be one-third to one-fifth as effective at improving wrinkles and hyperpigmentation.[96]

Vitamin C is a potent water-soluble nonenzymatic antioxidant that has the capacity to rejuvenate photoaged skin following its topical application.[100] One of the main difficulties with vitamin C products is instability.[101] The most stable formulation of vitamin C is L-ascorbic acid with a pH of 3.5, as acidity improves its penetration and stability. When used topically, ascorbic acid can significantly improve photoageing scores for cheek and the perioral area,[100] and reduce skin roughness and wrinkling.[102] These clinical improvements are thought to be mediated via the proliferation of keratinocytes and fibroblasts,[103] increased expression of collagen I and collagen III,[100,102,104] newly synthesized elastic fibres in the papillary dermis,[105] and also increased expression of ECM protease inhibitors such as TIMPS.[104] In addition to increased expression of collagen, topical ascorbic acid also improves collagen fibre organization and cross-linking, which together enhance the strength and stability of the ECM.[106] Vitamin C is also a potent cosmeceutical for the treatment of hyperpigmentation. Vitamin C is thought to inhibit the enzyme tyrosinase (responsible for the conversion of tyrosine to melanin) by interacting with copper ions at tyrosinase active sites, thus reducing melanin synthesis.[101,107] Therefore, topical vitamin C has some value in improving the pigmentary changes associated with sun exposure,[108] but high-quality clinical trial data are lacking.

Conclusion

Skin ageing is inevitable, but measures can be taken to reduce the impact, particularly changes that are caused by environmental factors. Prevention of UVR-induced accelerated skin ageing, with the regular use of broad-spectrum photoprotection, should be an integral part of the skincare routine. This can be supplemented with topical antioxidant products that provide additional photoprotection, and may also help to neutralize other sources of oxidative stress, such as air pollution. Optimization of barrier function with the use of simple emollients can also play a role: a healthy stratum corneum is the first line of defence against environmental assault. Topical retinoids and some peptides, in addition to epidermal effects, demonstrate dermal repair with a more profound clinical impact on deeper cutaneous wrinkles, although cellular changes will take months, not days.

A myriad of other 'active ingredients' are available in the marketplace, with variable levels of scientific evidence to support claims. Preferences of skincare regimes cover a broad range and may have deep-seated cultural and personal influences. Therefore, professional advice should remain objective and evidence-based but not judgemental. Topical rejuvenation strategies remain at the lower end of the risk-spectrum compared with more invasive injectable, device-based and even surgical options. Sensible

and reassuring advice can have a profound effect on our patients' overall wellbeing, particularly in those vulnerable to insecurity, anxiety or fear of 'missing out.'

Furthermore, realistic expectations with regard to overall impact on facial morphology are needed, as even the best skin rejuvenation programme will not mitigate potentially more dramatic volumetric changes due to underlying fat redistribution, atrophy and deeper bone loss. As dermatologists we can support our patients by promoting the concept of 'skin health' (as opposed to 'antiageing') in order to help maintain a positive perspective toward skin appearance and the effects topical products can achieve.

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Conflicts of interest

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