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Review

The human skin, its ageing process, and current anti-ageing cosmeceutical products

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The skin is the largest, outermost, and one of the most important organs of the human body, acting as a protective barrier that encloses internal organs. Among its many crucial roles, it serves as a medium through which the body perceives the external environment. Skin ageing, which results from a systematic reduction in the number and size of cells in the layers that constitute the skin, is one of the earliest manifestations of human ageing, with facial skin being the first to reveal these signs. The anti-ageing cosmetic industry, driven by factors such as an ageing population, increasing consumer awareness about skincare, and advancements in cosmetic technology, remains a significant sector within the broader beauty and skincare market. While several current anti-ageing products claim to reduce the appearance of wrinkles, fine lines, and other signs of cutaneous ageing, the effectiveness and safety of these products, particularly across different ethnicities and skin types, remain largely unknown due to limited research. Nevertheless, continuous innovations in active ingredients, excipients, formulations, and delivery systems have led to the development of a wide range of anti-ageing products, including creams, serums, masks, and devices. This review examines some of the current literature on active ingredients used in skin anti-ageing products.

Key words: Anti-ageing, cosmetics, cosmeceuticals, ingredients, bee venom, skin.

INTRODUCTION

Ageing of the human body is a natural process, the features of which first become apparent on the skin, especially on the face (Sadick et al., 2009; Ramos-e-Silva and Carneiro, 2001). Signs of facial ageing begin to appear as early as the third decade of life—about 3 to 4 decades earlier than they do on unexposed areas, such as the abdomen.

Cutaneous ageing results from a systematic reduction in the number and size of cells in the layers that make up the skin, as well as from the slowing down of many of the skin's organic functions. Biological functions that slow down with ageing include the skin's ability to replace lost cells, respond to injury, maintain barrier function, clear chemicals, perceive sensations, mount immune and vascular responses, produce sweat, regulate temperature, and synthesize vitamin D and sebum (Ramos-e-Silva and Carneiro, 2001). These biological changes lead to alterations in the aesthetic appearance of the skin, skeletal support structures, and soft tissues (Sadick et al., 2009). These features are also accompanied by an increase in the size and distribution of pores (Mizukoshi and Takahashi, 2014).

The process of skin ageing is a complex one, which is both inevitable and irreversible, but the appearance of its

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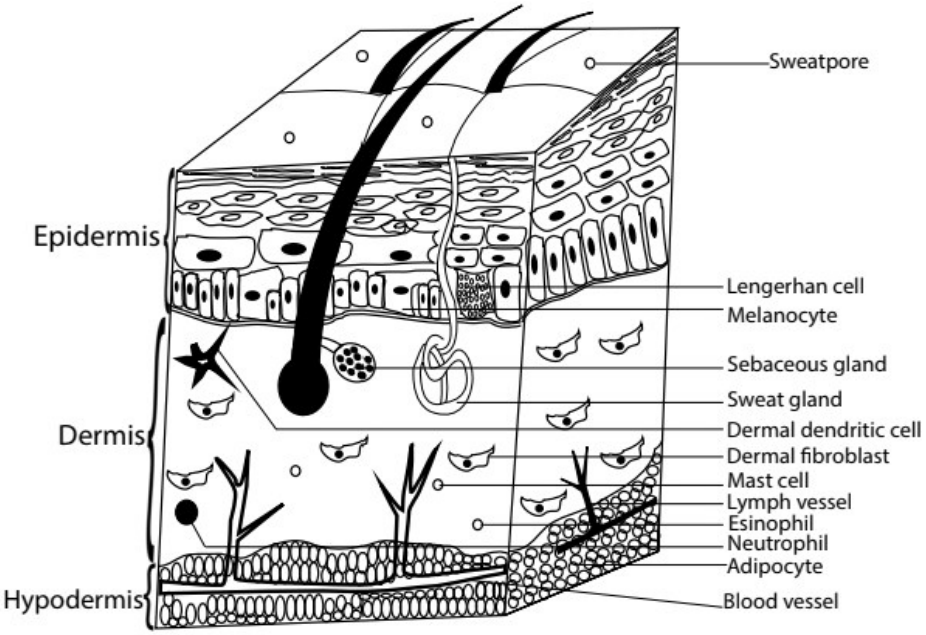

Figure 1. Structure of the human skin showing cell populations. The three main layers—the epidermis, dermis and hypodermis—are also shown.
Source: Kendall and Nicolaou (2013).

symptoms can be slowed or masked. These symptoms include wrinkles, a leathery texture, mottled pigmentation, laxity, and sallow discoloration (Fisher et al., 1999). Others include irregular pigmentation, telangiectasia—defined as "small clusters of widened blood vessels on the skin, often spidery in appearance"—and a variety of neoplasms of varying degrees of malignancy (El-Domyati et al., 2002). Since early-onset skin ageing is primarily due to sun exposure, cosmetic anti-ageing interventions must aim at blocking the skin's uptake of UV rays while simultaneously restoring the biochemical processes that lead to the restoration of the skin's histological integrity, resulting in a more youthful appearance.

SKIN PHYSIOLOGY

Being the outermost part of the body that encloses internal organs, the skin acts as a medium through which the body perceives the external environment. It serves as a barrier against the passage of certain materials into or out of the body, depending on the body's homeostatic or defensive requirements (Staff, 1978). The skin protects against the invasion of disease-causing organisms (such as bacteria) and harmful substances (such as chemical irritants), thus forming part of the innate immune system and serving as a first line of defense for the body. It also plays a role in thermoregulation by controlling the production and loss of water through sweat during homeostasis. Through melanin production, the skin ensures that just the right amount of light needed for vitamin D production—which is essential for bone tissue—penetrates the deeper layers without causing damage to the underlying tissues (Staff, 1978).

The skin consists of three main layers: (i) the epidermis, which is the outermost layer, (ii) the dermis, often referred to as the "true skin," and (iii) the hypodermis, which is largely made up of subcutaneous fatty tissue (Figure 1) (Arda et al., 2014).

The epidermis

The epidermis contains pigment-producing melanocytes which produce melanin thus determining the shade or colour of the skin. It is divided into five different functional sub-layers (strata) which are (from outermost to innermost): stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale (Figure 2). The innermost layers contain young, actively dividing and growing keratinocytes which gradually flatten as they get pushed to the outer layers by newer cells underneath them. This flattening occurs concomitantly with exocytotic extrusion of lipids and complete cornification to become corneocytes, so that the outermost layer (stratum corneum) consists exclusively of dead keratinized cells in an amorphous matrix containing proteins and fats (Staff, 1978; Lodén, 2003).

Cells on the surface of the stratum corneum continually get sloughed off (Rawlings, 2014); sloughed-off cells are replaced by smoother, newly cornified cells beneath them to maintain a state of balance in the epidermis. However,

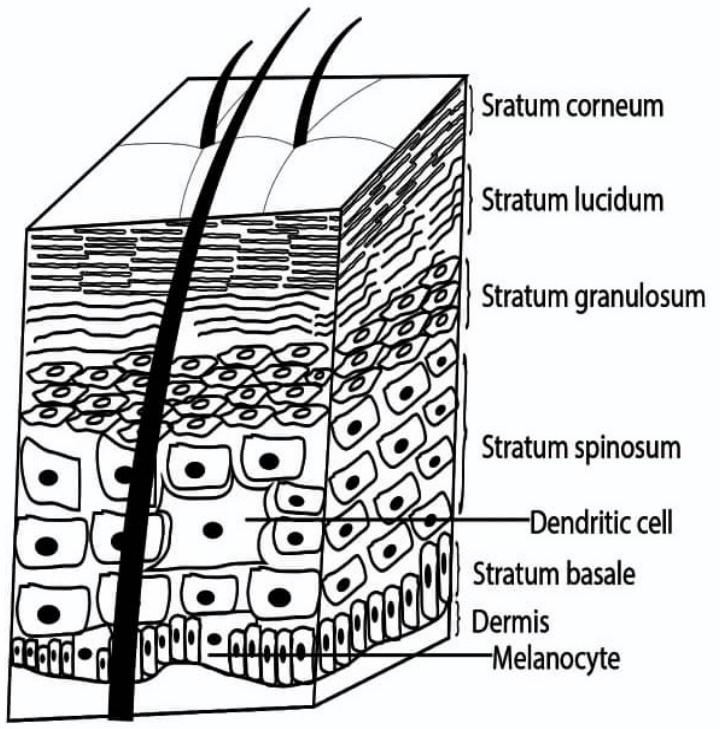

Figure 2. Structure of the epidermis of the human skin.

this balance can be disrupted due to impaired physiological function of the skin (such as atopic dermatitis) (Lodén, 2003), and naturally slows down with skin ageing. In the normal skin, complete epidermal renewal takes approximately 28 days (Stiefel and Schwack, 2014). Exfoliating and keratolytic agents such as glycolic and salicylic acids, which are respectively alpha and beta hydroxy acids, act by reducing the adhesion of corneocytes in the stratum corneum thus accelerating the sloughing off of dead cells (Ramos-e-Silva and Carneiro, 2001; Stiefel and Schwack, 2014). This exfoliating property, leading to a smoother and softer sensation of aged skin, is a key marketing claim for a variety of cosmetic formulations (Draelos, 2008). Table 1 summarizes the features and functions of the 5 sublayers constituting the epidermis.

The dermis

The dermal layer of the skin is separated from the stratum basale of the epidermis by a basement membrane. Fibroblasts are the principal cells found in this layer. Their role is to secrete extracellular matrix (ECM), and they also produce collagen and elastin, the principal fibrillous connective tissue of the skin responsible for maintaining its mechanical stability and resilience (Teti, 1992). Collagen is the most abundant structural protein in connective tissue (Min et al., 2004), and although there are several forms of the protein in the skin, type 1 is the most abundant, comprising approximately 90% of its dry weight (Takasao et al., 2012).

The dermis also contains sebaceous glands, hair follicles, sweat glands and apocrine glands all of which provide homeostatic functions to the skin and body Kendall and Nicolaou (2013); Stiefel and Schwack (2014). Numerous blood and lymphatic vessels are present which supply nourishment to dermal and epidermal cells and carry away toxic wastes for removal via an excretion process. In addition to the fibroblasts, immune cells are also present. The immune cells found in the dermis include dendritic cells, monocytes/macrophages, lymphocytes, neutrophils, T cells, B cells, eosinophils, and mast cells (Figure 1). These provide routine surveillance of the blood vessels in the dermis and will infiltrate cutaneous tissues during inflammation, after stimulation by inflammatory mediators such as cytokines (such as TNF- α and interleukins IL-1, IL-6) and bioactive lipids, leading to a cutaneous immune cell population (Kendall and Nicolaou, 2013). The dermis consists of both the papillary layer (stratum papillare) and the reticular layer (stratum reticulare) (Stiefel and Schwack, 2014).

The hypodermis

The hypodermis or subcutaneous tissue is the innermost layer of the skin containing mainly adipocytes, larger blood

Table 1. A summary of the layers of the human skin epidermis.

Layer	Features and functions	References
Stratum basale	Highest mitotic activity of the skin layers. Composed mainly of keratinocytes, both proliferating (stem cells) and non-proliferating. Continuous cell division of proliferating keratinocytes results in corneocytes that are exfoliated at the skin surface. Base cells have large nuclei, numerous free ribosomes, few mitochondria, small Golgi apparatus, and a rough endoplasmic reticulum. Several Merkel cells (tactile cells or touch receptors) and melanocytes are located in this layer.	Mistry et al. (2012) and Reed et al., (2013)
Stratum spinosum	It is the thickest layer of skin. It consists of multilayered cells formed from the gradual transformation of keratinocytes to become larger, polygonal and flattened in the outward part of the layer. Cells in this layer synthesize cytokeratins (intermediate filaments), which are grouped into bundles known as tonofilaments. Keratinocytes are linked to each other by multiple, prickle-shaped intercellular bridges (desmosomes) where the tonofilaments are anchored to the cell membrane. The resulting reticulate structure accounts for the typical name. Langerhans cells which play a role in the immune system are located in this layer.	Brody (1960), Allen and Potten (1975), Girolomoni et al. (1990), Stingl et al. (1977), and Romani et al. (1989)
Stratum granulosum	There is increased synthesis of keratohyalin in keratinocytes in this layer which initiates the process of their cornification/keratinization. In addition, loss of cell organelles such as nuclei occurs. Lipids in the lamellar bodies are released to form the skin lipid barrier.	Arda et al. (2014) and Elias (2012)
Stratum lucidum	Present only in the skin of the palms and soles of feet, the stratum lucidum forms a clear and thin layer of dead cells covering the stratum granulosum.	Arda et al. (2014)
Stratum corneum	This cornified/horny layer consists of 10-30 layers of enucleated polyhedral corneocytes. These are embedded in a matrix of cornified proteins, including loricrin, involucrin and flaggrins, which are filled with keratin that gives them their water-retaining properties. Corneocytes are “glued” to each other through corneodesmosomes and the surrounding hydrophobic lipids. The stratum corneum accounts for most of the barrier functions of the epidermis by preventing water loss from the body and acting as an impermeable layer for excluding foreign substances.	Arda et al. (2014) and Elias (2012)

vessels and nerves. It acts as the layer that attaches the skin to underlying tissues such as bone and muscle. The main cells present in the subcutaneous tissue are fibroblasts, adipocytes and macrophages. The adipose tissue acts as a store for energy and free fatty acids. At the same time, a range of bioactive mediators for cutaneous cell functions are produced here. For example, fibroblast function in the dermis of the skin is impaired by free fatty acids (FFAs), such as palmitic acid, released by abnormally enlarged adipocytes resulting in impairment of fibroblast proliferation which consequently affects collagen and elastin production. The negative influence of palmitic acid on fibroblast proliferation was shown to be counteracted by supplementation with eicosapentaenoic acid (EPA), an inhibitor of Toll-like receptors (TLRs), which suggested that enlarged adipocytes possibly decreased the function of dermal fibroblasts through activation of TLRs by secreted FFAs (Ezure and Amano, 2011). Adipocytes are also a source of peptide hormones known as adipokines which regulate various local and systemic effects such as inflammation, insulin sensitivity, fat storage, and appetite regulation (Falcao-Pires et al., 2012). In addition, the adipose tissue has recently been identified as a key source of stem cells with the potential to accelerate keratinocyte proliferation and migration, as well as dermal fibroblast proliferation and contraction (Moon et al., 2012; Lee et al., 2012)—processes which can augment wound healing and reverse the effects of ageing skin.

MECHANISMS OF SKIN AGEING

It is generally known that skin ageing is caused by both genetically determined (intrinsic) factors that are mediated via hormones and other biochemical processes, as well as environmentally determined (extrinsic) factors that largely result from exposure to UV radiation, leading to skin damage and loss of its integrity (Sadick et al., 2009). While intrinsic and extrinsic ageing result in distinct histological features, the main functional changes are similar (Sadick et al., 2009). For instance, intrinsic ageing leads to loss of elastic tissue and reduction in number and size of cells (Gunin et al., 2011, 2014a, 2024b) but extrinsically

damaged skin features elastosis and increased numbers of mast cells, fibroblasts and histiocytes (Sadick et al., 2009). Thus, intrinsic ageing generally demonstrates overall loss of extracellular matrix while photo-ageing demonstrates selective increases, especially of elastin. However, both types of skin ageing share functional features which include reduced melanocyte and collagen content and impaired wound healing, although these features may be more marked in photo-damaged skin.

Intrinsic ageing

Intrinsic or innate skin ageing has been called the “biologic clock”-type of ageing (El-Domyati et al., 2002) which affects the skin in a similar way that it affects internal organs—that is, in a slow, irreversible manner. The ageing is associated with gradual loss of homeostatic, structural and functional processes modulated through gene expression of which Sirtuin 6 (SIRT6) is a recently identified regulator (Sharma et al., 2013). Whereas photo-ageing affects mainly areas exposed to the sun such as the face, intrinsic ageing takes place even in sun-protected areas leading to a progressive decrease in the amount of elastic and collagen tissues (El-Domyati et al., 2002). Histopathological features (Table 2) are particularly demonstrable during the 8 and 9th decades of human life, implying that features of intrinsic ageing are much more gradual compared to those of photo-ageing which begin to appear around the 3rd decade.

Intrinsic features of ageing (Table 2) may be attributed to increase in catabolic processes coupled with decreased anabolism in relation to dermal collagen and elastin fibres produced by fibroblasts in the reticular dermis of the skin. It has also been suggested that the growth capacity of fibroblasts decreases with age even in sun-protected skin. At the same time the rate of expression of elastin gene in fibroblasts markedly reduces around the 4th or 5th decade of life. Both these factors reduce the capacity for collagen and elastin synthesis by fibroblasts. This occurs hand in hand with an increasingly abnormal expression of matrix metalloproteinases which lead to increased degradation of the collagen fibres. Altogether these processes lead to dermal atrophy and the appearance of fine lines that portray intrinsically aged skin. In addition, the matricellular protein, periostin, which is produced by fibroblasts and non-follicular skin-derived precursors, has been shown to play a role in the homeostasis and proper assembly of collagen. When this protein is down-regulated as occurs in ageing skin, it leads to increased susceptibility of collagen towards proteases which contributes to the observed features (Egbert et al., 2014). The main structural differences between young skin and skin that has undergone intrinsic and photo-ageing are summarized in Figure 3. Young skin shows a balanced distribution of keratinocytes in the multi-layered epidermis (E) and in the dermis (D), and the ECM components are quite distinct.

Skin that has aged intrinsically shows both epidermal and dermal atrophy. Collagen and elastin in the extracellular matrix are reduced, while the amount of cross-linkages in collagen fibres rises. The net number of fibroblast cells reduces; the few remaining ones reveal a more senescent morphological and functional phenotype, with elevated release of matrix-degrading metalloproteinases (MMPs). On the other hand, photo-aged skin is hyperplastic with an increased thickness of the stratum corneum (H), epidermis (E) and the dermis layer (D). The epidermis presents with significant roughness and dryness. Melanocyte distribution becomes increasingly inhomogeneous resulting in pigmentary changes. There is a reduction in the number of anchoring fibrils that link the epidermis to the dermis. Interstitial collagen is severely damaged and reduced as well. Elastosis and an increase in microfibrillar components lead to a severely disorganized supramolecular structure that is almost dysfunctional. In the long term continued sun exposure leads to heliodermatitis, an inflammatory state associated with increased numbers of mast cells and mononucleocytes (Wlaschek et al., 2001).

Extrinsic ageing

The ultraviolet radiation from the sun can be subdivided into four different wavelength ranges: UVC, which is less than 290 nm wavelength (λ), UVB (λ=290-320 nm), UVA2 (λ=320-340 nm), and UVA1 (λ=340-400 nm) (Figure 4). All UVC and majority of UVB are absorbed by the ozone layer which is present in the earth’s stratosphere. The most damaging biological effects of ultraviolet radiation are due to residual UVB that fails to get absorbed in the earth’s stratosphere, although UVA2 penetrates the skin more deeply and also contributes to photo-ageing (Fisher et al., 1998). Other extrinsic factors for skin ageing include tobacco smoking (Bernhard et al., 2007; Lotfi et al., 2014) and climatic factors such as wind, humidity, pollution, and high temperatures (Singh and Maibach, 2013).

It has been suggested that the main mechanism by which exposure to UV radiation induces premature skin ageing is via up-regulation of the transcription factor activator protein (AP)-1, and the induction of AP-1-regulated matrix metalloproteinases (MMPs), including collagenase, stromelysin and 92-kD gelatinase, that significantly degrade skin collagen (Fisher et al., 1999, 1998). At the same time, inhibition of pro-collagens type I and type III, at least partly due to induction of c-Jun, interferes with the process of transcription of pro-collagen (Fisher et al., 2000). Both these mechanisms that is induction of collagen degradation and inhibition of synthesis of its precursor, pro-collagen, can be overcome through *in vivo* pre-treatment of skin with all-trans retinoic acid (Fisher et al., 1999, 1998, 2000), at least 16h prior to exposure to the sun, thereby retarding the process of premature ageing.

Table 2. Changes associated with intrinsically aged skin.

Intrinsic features of ageing	Consequences	Reference
Flattening of the epidermal-dermal interface	Decreased surface contact area and higher risk of layers being separated by shearing forces	Staff (1978) and Lodén (2003)
Abnormality or loss of dermal papilla structures	Decreased surface contact area and higher risk of layers being separated by shearing forces	Mizukoshi et al. (2014)
Dermal atrophy resulting in loss of thickness	Reduced strength and resiliency	Egbert et al. (2014)
Loss of elastic tissue in the fine subepidermal elaunin network	Sensitization to deformational forces, fine wrinkle formation	Gunin et al. (2011, 2014a, 2014b)
Irregular thickening, fragmentation and disorganization of elastic tissue network in the reticular dermis	Dermal deformation and loss of skin firmness leading to wrinkles	
Increase in heterogeneously sized basal cells	Increased vulnerability and fragility	Egbert et al. (2014)
Atrophy of the stratum spinosum	Increased vulnerability and fragility	
Thinning of the epidermis by 10-50%	Increased vulnerability and fragility	
Reduction of fibroblasts	Reduced strength and resiliency	Ezure and Amano (2011)
Decreased in the number of Langerhans cells	Reduced immune functions in cutaneous tissue	Sadick et al. (2009), Mizukoshi et al. (2014), and Zouboulis and Makrantonaki (2011)
Reduced melanocyte activity due to decrease in number and increase in their heterogeneity	Greying of hair, guttate amelanosis and lentigines	Sadick et al. (2009), Mizukoshi et al. (2014), Wlaschek et al. (2001)
Atrophy of the extracellular matrix	Reduced strength and resiliency	Sadick et al. (2009), Mizukoshi et al. (2014) and Zouboulis and Makrantonaki (2011)
Reduced production of type I and type III collagens	Fine wrinkle formation	Ezure and Amano (2011)
Reduction and disintegration of collagen and elastic fibres, deposition of exogenous substances (such as amyloid P)	Sensitization to deformational forces, fine wrinkle formation	
Decreased mitotic activity, increased duration of cell cycle and migration time; lower epidermal turnover rate	Decreased desquamation and delayed wound healing	
Decreased hyaluronidase protein expression and thus impaired cleavage of hyaluronan (Reed et al., 2013)	Decreased wound healing ability, perhaps due to decreased cleavage of hyaluronic acid from decreased (Reed et al., 2013)	
Slow replacement of lipids	Disturbed barrier function	Sadick et al., (2009), Mizukoshi et al. (2014), and Zouboulis and Makrantonaki (2011)
Reduced cutaneous microvasculature	Low cutaneous vascular responsiveness, disturbed thermoregulation, and reduced nutrient supply of skin	
Decrease in size/number and function of skin appendages such as sebaceous glands, sweat glands, apocrine glands	Decreased lipid and sweat production, disturbed re-epithelization of deep cutaneous wounds	
Thinning of subcutaneous fat	Reduced insulation and energy production	
Reduction of nerve endings	Disturbed sensory function	

Source: Flynn et al. (2001), Draelos (2008) and Mistry et al. (2012).

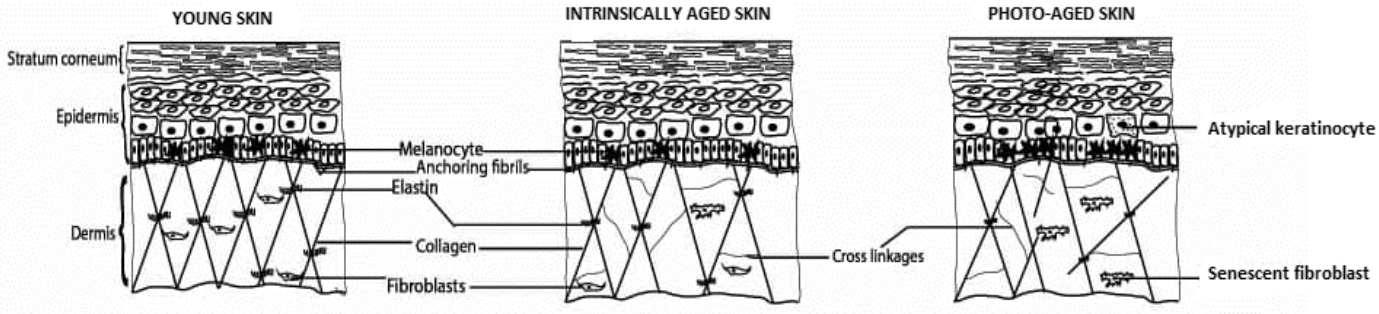

Figure 3. Features characteristic of young, intrinsically aged and photo-aged skin. The figure was reproduced with modifications from a previous paper.
Source: Wlaschek et al. (2001).

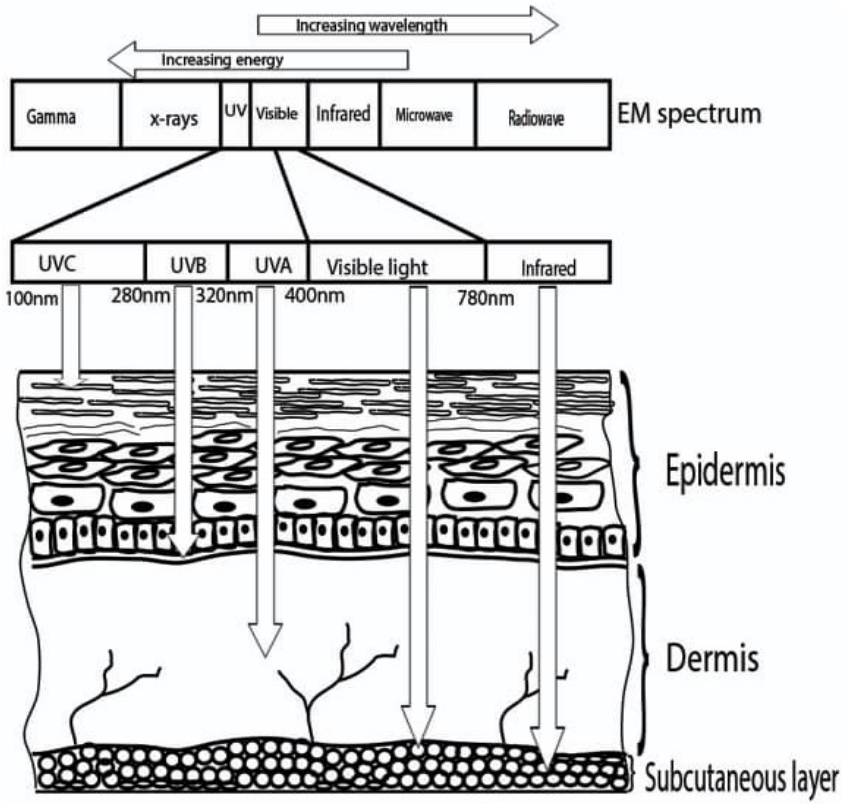

Figure 4. A section of the sun's electromagnetic radiation showing the wavelength range of electromagnetic radiation and its transmittance through the skin. The figures were reproduced with modifications from a previous paper.
Source: Stiefel and Schwack (2014).

Production of oxidant free radicals in the form of reactive nitrogen or oxygen species in the skin is an inevitable consequence of physiological metabolism. The most common reactive species in the body are superoxide ions (O_2-), nitrogen monoxide free radicals (NO.) and hydroxyl radicals (OH.). Other species of biological importance are hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), singlet oxygen, and peroxynitrite (Wolfle et al., 2014). The harmful effects of reactive molecule species are mediated through the impairment of DNA structure and function, leading to damage of enzymes and cellular structures, and interference with specific signaling pathways in cell metabolism. The body's physiological protection mechanisms include enzymatic and non-enzymatic

antioxidant defense systems such as catalase, glutathione, ascorbic acid, and α-tocopherol (Rhie et al., 2001) which are able to keep these harmful substances largely neutralized in a normal body state. However, exposure of the skin to pollutants and UV irradiation produces additional oxidants which eventually overwhelm endogenous protection mechanisms and cause early skin ageing in addition to other skin problems such as immune impairment and cancer. The morphological features of photo-aged skin are shown in Table 3. It should be noted, however, that reactive molecular species also trigger metabolic processes that lead to cellular homeostasis, growth and development, immune defense, cell and tissue repair, and apoptosis. The use of antioxidants in cosmeceutical formulations can augment the body's mechanisms to restore the balance between oxidative and anti-oxidative mechanisms in the skin (Wolfle et al., 2014).

ROLE OF GLUCOCORTICOIDS

Glucocorticoids (GCs) are potent inhibitors of inflammation whose actions are mediated either through direct binding of the GC/GC-receptor complex to GC-responsive elements in the promoter region of genes, or indirectly through binding of the complex to other transcription factors such as activating protein-1 (AP-1) and nuclear factor-kappaB (NF-κB). GCs inhibit many pro-inflammatory mediators such as cytokines, chemokines, metabolites of arachidonic acid, and adhesion molecules while at the same time up-regulating anti-inflammatory mediators (Van Der 1998). Current evidence suggests that changes in tissue-specific pre-receptor regulation of local glucocorticoid (GC) availability by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) may explain the phenotypic link between GC excess (such as occurs in Cushing's disease) and ageing skin. The role of 11β-HSD1 in intact cells is exclusively limited to NADPH-dependent oxo-reduction of cortisone to form the active form cortisol (Tiganescu et al., 2011). Expression of 11β-HSD1 has been characterized in both human and rodent skins, where increased expression of 11β-HSD1 was found in primary human dermal fibroblasts (HDFs) donated from older skins, and in donor-matched photo-exposed skin compared to photo-protected ones. This observation has led to suggestions that increased capacity for local GC activation may represent a novel mediator of age-related changes in the physiology, function, and appearance observed in both intrinsically and extrinsically aged skin phenotypes (Tiganescu et al., 2011, 2013). Inhibition of the 11β-HSD1 enzyme in mice was demonstrated to prevent age-associated dermal atrophy leading to improved collagen density and restoration of its structural organization, suggesting a novel application of these inhibitors in the treatment of age-related dermal malfunction and enhancement of wound healing (Tiganescu et al., 2013).

ROLE OF OESTROGENS

Recent studies suggest that the observed deterioration of skin in peri-menopausal women may be partly due to declining oestrogen levels. The decline in oestrogen level is thought to lead to decreased rates of collagen production due to the effects of oxidative stress caused by reactive oxygen species (ROS) (Bottai et al., 2013). Oestrogens have been reported to exert anti-oxidant and vaso-protective effects in vascular smooth muscle cells through diminished free-radical production mediated via upregulation regulation of superoxide dismutase (SOD) expression and enzyme activity (Strehlow et al., 2003). The SOD enzyme catalyses the dismutation of cell-damaging superoxide (O_2-) radicals into less damaging hydrogen peroxide (H_2O_2) or molecular oxygen (O_2), thus protecting the cells from oxidative stress induced by these radicals. This oxidative stress results in damage to cellular membranes and the structure of nucleic acids, resulting in loss of cell viability (Wolfle et al., 2014). Another study with 17β-estradiol demonstrated restoration of collagen production in fibroblasts and improved viability of HaCaT cells (keratinocytes) by blocking the effects of H_2O_2-mediated oxidative cell damage. This demonstrated the effectiveness of oestrogen in restoring dermal integrity and improving skin appearance (Bottai et al., 2013).

CLINICAL AND PHYSICAL FACIAL AGING

A combination of both histological and functional changes in the skin gives rise to structural changes that slowly begin to appear on the skin as early as one's third decade of life when soft tissue facial structures begin to weaken (Table 4).

Anti-ageing approaches

General approaches

Because skin wrinkling is mainly due to volume loss in the cutaneous tissues, any cosmetic application that improves skin hydration will have at least some minimal effect on improving skin appearance. Cutaneous hydration can be improved by reducing trans-epidermal water loss (TEWL) through the use of occlusive agents (such as petrolatum or lanolin) or by using agents with water adsorbing properties such as humectants (such as glycerin or honey) and hydrophilic matrix agents (such as proteins) (Table 5) (Lotfi et al., 2014; Rudikoff, 1998). A recent systematic review on the effectiveness of hyaluronic acids injections in the improvement of facial skin hydration, firmness, brightness, texture, radiance, and elasticity found promising results (Ghatge and Ghatge, 2023). Incorporation of ceramides into cosmetic formulations aids in improving the skin barrier function

Table 3. Changes associated with extrinsically aged skin.

Morphological features of photo-aged skin	References
Thickened basement membrane	Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
Generally inflamed with dilated, tortuous blood vessels	El-Domyati et al., 2002; Wlaschek et al., 2001; Yaar et al., 2001
Increased populations of mast cells, histiocytes, and fibroblasts	Sadick et al., 2009; Yaar et al., 2001
Impaired proliferation, differentiation, desquamation, and apoptosis of keratinocytes	Sadick et al., 2009; Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
The epidermis shows an acanthosis and mild hyperkeratosis, which clinically presents as roughness and dryness.	Sadick et al., 2009; Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
Dermal elastosis (overgrowth of abnormal elastic fibres) due to UV-mediated damage to dermal fibroblasts	Sadick et al., 2009; Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
Abnormal elastin production	El-Domyati et al., 2002; Yaar et al., 2001
Prolonged breakdown of extracellular matrix by proteases elicited by inflammatory mediators.	El-Domyati et al., 2002; Egbert et al., 2014
Increased levels of dysfunctional glycosaminoglycans and proteoglycans	Sadick et al., 2009; Mizukoshi et al., 2014;
Hyper-plasticity with an increase in the thickness of the horny layer (H), the epidermis (E) and the dermal compartment	Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
Degeneration of collagenous meshwork, increased collagen degradation	Sadick et al., 2009; Yaar et al., 2001
Stellate phenotype of fibroblasts and increased biosynthetic activity	Mizukoshi et al., 2014; Zouboulis and Makrantonaki 2011
Impairment of wound healing Reduction of melanocyte activity	Sadick et al., 2009; Yaar et al., 2001
Distribution of the melanocytes becomes inhomogeneous resulting in pigmentary changes ranging from pigmented maculae (solar lentigines) to areas of hypopigmentation (guttate hypomelanosis)	
Anchoring fibrils which connect the epidermis with the dermis are reduced in number, and also interstitial collagen is reduced and severely damaged.	Wlaschek et al., 2001
There is an increase in elastic fibres and the microfibriliar components resulting in a non-functional severely disturbed supramolecular structure.	
State of inflammation (heliodermatitis) with an increase in mononuclear cells and mast cells.	
Flattening of the dermo-epithelial junction, reduction of anchoring fibrils	Sadick et al., 2009; El-Domyati et al., 2002; Yaar et al., 2001

and replenishing skin ceramides which, along with free fatty acids and cholesterol, play the “mortar” role to the corneocytes’ “brick” in the “brick and mortar” theory of the stratum corneum (Rawlings, 2014). By forming a film over the surface of the skin, hydrophilic matrices (such as proteins) in cosmetic formulations impede trans-epidermal

Table 4. Structural features of aged skin.

Facial area	Structural and functional features	References
Upper third	Drooping of eyebrows due to reduced skin elasticity, the action of force of gravity, and repeated periorbital muscular contraction. Excess lid folds lead to an aged and tired facial appearance due to loss of elasticity in the skin of the upper eyelid. Fine deep horizontal lines on the forehead and vertical rhytides on the glabella due to repeated contraction of the frontalis, procerus, and corrugators supercilii muscles Exposed bony orbital rims due to recession of the soft-tissue prominences near the cheeks Appearance of excess fat in the lower eyelid due to loss of soft tissue over the orbital rims.	Sadick et al. (2009) and Friedman (2005)
Middle third	Development of a palpebronasal groove and thinning of subcutaneous fat due to the ageing process. Prominent nasal fold due to weakening of the malar and orbital ligaments resulting in the descent of the malar fat pad and its overlap with the more firmly attached ligaments of the cheek-lip groove.	Sadick et al. (2009) and Binder and Azizzadeh (2008)
Lower third	Development of vertical rhytides above the vermilion border due to thinning of the skin in the area. Elongation of lips and their loss of fullness. Accumulation of excess skin and soft tissue near the jaws and chin obscures the well-defined jawline of youth and gives rise to jowls. This results from volume loss and laxity of ligaments and skin in the malar and perioral areas.	Sadick et al. (2009), Perkins and Sandel (2007), Zins and Moreira-Gonzalez (2006), and Perkins et al. (2007)

Table 5. Categories of common cosmetic ingredients.

Activity	Ingredients	Actions	References
Occlusive agents	Petrolatum, dimethicone, mineral oil, vegetable oils, waxes, lanolin.	Oily substances that act as barrier on the skin to water loss. Petrolatum blocks up to 99% of water loss from the surface of the skin; it is the gold standard for skin moisturisation. It smells bad, feels sticky and can stain clothes. Prevention of TEWL leads to improvement of fine line of dehydration especially apparent around the eyes.	Draelos (2008, 1995)
Humectants	Glycerin, honey, sodium lactate, urea, propylene glycol sorbitol, pyrrolidone carboxylic acid, gelatin, hyaluronic acid, Vitamins, some proteins.	Rehydrates stratum corneum leading to reduction in fine wrinkling. Once applied onto the surface of the skin, humectants attract water and hold it in a sponge-like manner. They act most effectively when in combination with occlusive to reduce appearance of fine wrinkles on the face, thus helping to substantiate anti-ageing claims.	Draelos (2008, 1995, 2009)
Hydrophilic matrices	Proteins, oatmeal bath, hyaluronic acid.	These large MW film-forming agents cause wrinkle reduction by reducing water escape from the skin through the thin film covering they form on application.	Draelos (2008, 1995, 2012)

water loss and increase the smoothness of the skin surface. Thus, products which incorporate occlusive agents and moisturizing agents will sometimes claim immediate reduction of wrinkled appearance through a

combination of better moisturisation and evenness of skin surface which is an anti-ageing claim (Draelos, 2008).

Sunscreens or UV filters

A sunscreen is a topical product that contains one or more UV filters, along with additional substances like surfactants, preservatives, and stabilizers (Mansour and Venero, 2021). The use of sunscreens is the most common approach for counteracting signs of skin ageing. By blocking harmful UVA and UVB radiation from the sun, sunscreens minimize the exposure of the dermis and deeper layers of the epidermis to photodamage (Geisler et al., 2021). UV filters can be inorganic (using a physical mechanism) or organic compounds (using a chemical mechanism) (Fivenson et al., 2021). Some key ingredients found in sunscreen products include:

1. Para-aminobenzoic acid (PABA) esters: Examples include ethylhexyl dimethyl PABA (8%) and ethoxylated ethyl-4-aminobenzoate (10%), which absorb UVB rays with little effect on UVA, thus protecting against sunburns. However, they have low photo-stability and can cause skin irritation, allergies, and contact dermatitis in some individuals (Pantelic et al., 2023).
2. Salicylic acid derivatives: These filters are photo-stable and are often combined with other photo-labile UVA filters, such as avobenzone. Examples include 2-ethylhexyl salicylate (5%) and homosalate (1.4%) (Directive, 2009).
3. Cinnamic acid derivatives: Used as UVB absorbers, these are considered a better alternative to PABA derivatives. Examples include isopentyl 4-methoxycinnamate, 2-ethylhexyl 4-methoxycinnamate, cinoxate, and octocrylene (Gunia-Krzyżak et al., 2018).
4. Benzylidene camphor derivatives: Examples include 4-methylbenzylidene camphor, benzylidene camphor sulfonic acid, camphor benzalkonium methosulfate, and terephthalylidene dicamphor sulfonic acid (Shaath, 2010).
5. Benzophenone derivatives and structural analogs: These include oxybenzone, sulisobenzone, dioxybenzone, hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl] benzoate, and bis-(diethylaminohydroxybenzoyl benzoyl) piperazine (BDBP) (Mao et al., 2022).
6. Dibenzoylmethane derivatives: Examples include avobenzone (3-5%) and ecamsule (Draelos, 2008).
7. Benzimidazole and benzotriazole derivatives: Examples include phenylbenzimidazole sulfonic acid (4-8%), disodium phenyl dibenzimidazole tetrasulfonate, drometrizole trisiloxane, and methylene bis-benzotriazolyl tetramethylbutylphenol (Gautam et al., 2022; Pniewska and Kalinowska-Lis, 2024; Santos and Esteves da Silva, 2015).
8. Triazine derivatives: These include ethylhexyl triazone, diethylhexyl butamido triazone, bis-ethylhexyloxyphenol methoxyphenyl triazine, tris-biphenyl triazine, and phenylene bis-diphenyltriazine (Bos and Meinardi, 2000).
9. Other ingredients: These include meradimate, polysilicone-15, and methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (MCE) (https://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=sunscreen-ecransolaire; accessed on 2 June 2023).

The incorporation of sunscreens into cosmetic formulations provides justification for some manufacturers to claim enhanced anti-ageing benefits for the skin. This is because, while the moisturizing benefits of the formulation are immediately apparent due to the softer feel and shinier appearance of the skin upon application, the photo-protection-related anti-ageing effects may take weeks or months to manifest. Given that UVA radiation is one of the greatest contributors to photo-ageing, broad-spectrum photo-protection in the UVA range of wavelengths offers the most anti-ageing benefits.

Use of retinoids

Retinoids are a group of compounds structurally similar to vitamin A (retinol) and are widely used in cosmetic products such as face and hand creams, body lotions, shower gels, shampoos, and conditioners, among others (Rousselle, 2017). They can be natural or synthetic. On the skin, retinoids modulate keratinocyte differentiation and proliferation, resulting in reduced microcomedone formation, which typically occurs in acne (Thielitz and Gollnick, 2008). Retinoids are also used to treat psoriasis, hyperpigmentation, and both photo-aged and intrinsically aged skin by increasing collagen synthesis, inhibiting its degradation, stimulating epidermal cell renewal, and providing direct immunomodulatory, antibacterial, pigmentation, and antioxidant effects. Naturally occurring retinoids include retinol, retinal, retinoic acid, retinyl esters, and beta-carotene (Zasada and Budzisz, 2019).

Products containing all-trans retinoic acid and its derivatives, including tazarotene (a second-generation retinoid), offer significant improvements in the appearance of fine wrinkles and help clear localized cutaneous spots of hyper- and hypo-pigmentation (Sadick et al., 2009). Retinoid therapy is considered the mainstay for the treatment of photo-ageing. Retinoid creams work by antagonizing c-Jun-mediated inhibition of procollagen transcription and by inhibiting the breakdown of pro-collagen types I and III by matrix metalloproteinases, including collagenase—processes induced by UV exposure (Fisher et al., 1999, 1998, 2000). Retinoic acid is the active form and must be derived from its precursors (such as retinol) (Figure 5) and derivatives (such as retinyl esters with fatty acids, like palmitic acid), which make up most retinoid formulations (Draelos, 2008). It should be noted that the body's conversion of some retinoids into retinoic acid is quite low, affecting their efficacy, and that retinoic acid itself can be irritating (Draelos, 2008).

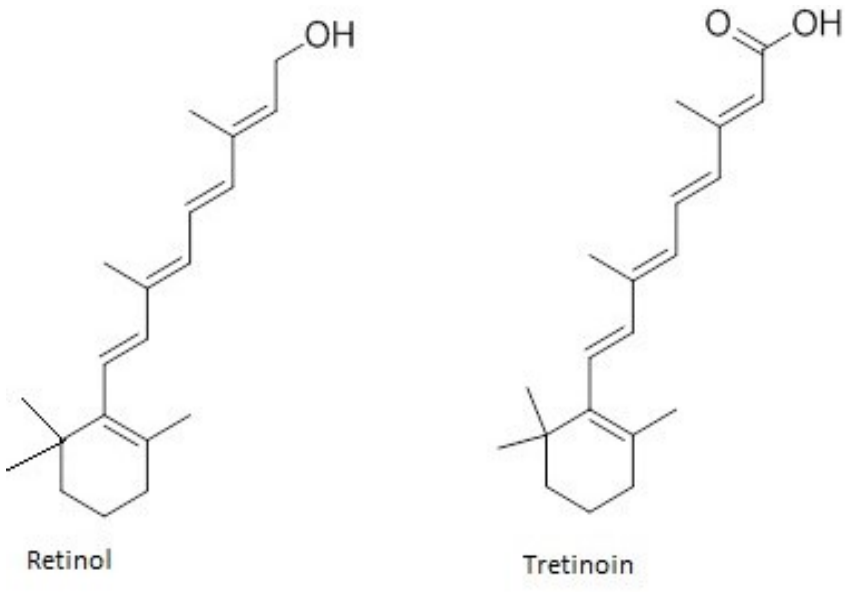

Figure 5. Structures of retinol and tretinoin. Tretinoin® is the synthetic form of retinoic acid which has demonstrated potent effects on aged skin (Orfanos et al., 1997) leading to increased collagen synthesis by fibroblasts.

Additionally, intact retinyl palmitate is a humectant with potent antioxidant properties. This multi-functionality makes retinoids popular among cosmetic formulators, particularly those targeting anti-ageing claims (Draelos, 2008). The overall effect of retinoids in cosmetic formulations is improved skin strength and resiliency, as well as increased water retention in the epidermal layer (Sadick et al., 2009).

It should be noted that tretinoin, tazarotene, adapalene, and trifarotene are prescription retinoids due to their higher efficacy compared to cosmetic retinoids such as retinoic acid. They also come with more adverse effects, including skin irritation, dryness, erythema, pruritus, and burning (Zasada and Budzisz, 2019).

Due to the risk of retinoid-associated phototoxicity, the Scientific Committee on Consumer Safety (SCCS) recommends that the retinoid concentration in cosmetics adhere to the following guidelines: Not exceeding 0.05% Retinol Equivalents (RE) in body lotions and 0.3% RE in hand and face creams, as well as other leave-on or rinse-off products (Rousselle, 2017). The French Agency accepts a maximum concentration of 0.15% RE, while Canada restricts it to 1% RE. However, the German Nutrition Society does not permit the use of vitamin A in all lip and body care products. Additionally, retinoic acid and its salts are prohibited in cosmetic products, regardless of concentration, due to their teratogenic effects. It is important to note that many anti-ageing cosmetics contain higher concentrations of retinoids than those recommended by the European Commission. When using such products concurrently with supplements or foods rich in vitamin A, there is a risk of vitamin A accumulation in the body. Accumulation can lead to adverse effects such as skin erythema, nausea, headache, abdominal pain, liver damage, and kidney damage (Rutkowski and Grzegorczyk, 2012).

Antioxidants

Free radicals are a major cause of skin ageing, as they damage DNA and promote various detrimental processes. Some of the ways antioxidants combat free radicals include scavenging them, suppressing the formation of Reactive Oxygen Species (ROS) which are involved in free radical generation, and protecting antioxidant defenses (Cao et al., 1997). Plants and their stem cells are excellent sources of antioxidants, such as polyphenols, phenolic acids, flavonoids, triterpenes, carotenoids, and peptides (Barbulova et al., 2014). Phenolic compounds possess redox properties that allow them to absorb and neutralize free radicals (Velioglu et al., 1988). An example of plant stem cell extracts with antioxidant properties is tomato stem cell extract, which is rich in flavonoids (rutin), phenolic acids (chlorogenic acid, coumaric acid, and protocatechuic acid), and beta carotene. The antioxidant activity of these compounds protects skin cells from oxidative stress and damage induced by heavy metals (Tito et al., 2011). Thus, anti- oxidants represent another avenue for delaying skin ageing. Topical antioxidants act as reducing agents for UV-induced oxygen free radicals produced during metabolism in the body, including in the skin, so as to render them unreactive. Some of these antioxidants include L-ascorbic acid (vitamin C), ferulic

acid, alpha-lipoic acid, kinetin, coffee berry, idebenone, coenzyme Q10 (Bentinger et al., 2010) and green tea (Sadick et al., 2009). Because free-radical production in the skin is exacerbated by exposure to UV radiation, antioxidants and retinoids may produce synergistic effects; thus their co-formulation into sunscreens should, in theory, lead to remarkable reduction in skin wrinkles.

Alpha hydroxyl acids

It has also been suggested that the long term use of α-hydroxyl acids (AHAs) in topical applications can improve skin wrinkling, reduce roughness and correct discoloration in photo-damaged skin. AHAs constitute a small group of low molecular weight organic acids including glycolic acid, citric acid, malic acid and ascorbic acid. While these agents are known for their exfoliating and degranulation properties, they may also lead to increased thickness of the epidermis, induce dermal collagen production, increase dermal perfusion, and improve moisture content of the epidermis. These processes eventually lead to improved skin elasticity and appearance. Because the efficacy of these agents relies on their use at high concentrations at low pH (<3.5), they are not currently available over the counter but only to by prescription from cosmetic dermatologists (Sadick et al., 2009). This limits their use in the general population as easily accessible alternative anti-ageing cosmetic ingredients. In addition, there are notable side effects that have been reported with continuous use of AHAs including mild skin irritation, redness, stinging or burning sensation upon application (Karwal and Mukovozov, 2023).

Use of Botox injections

Botulinum toxin (Botox) is produced by the bacterium *Clostridium botulinum*. It is a neurotoxin that upon local injection causes temporary muscle paralysis (denervation) by preventing transmission of impulses at the neuromuscular junctions (NMJ) of peripheral cholinergic neurons, thus resulting in relaxation (Benedetto, 1999; Monheit et al., 2007; Huilgol et al., 2009). Botox has no intrinsic effects on the skin's metabolic state that would fit the description of an anti-ageing effect. However, when injected into facial muscles, Botox smooths the skin overlying them, thus providing some relief of the wrinkled appearance of aged skin. Botulinum toxin A (Botox Cosmetic, Allergan Inc., USA) is licensed by US-FDA for managing moderate to severe glabellar lines in individuals who are 65 years or younger, although it also improves other facial lines especially dynamic lines and wrinkles in the upper third of the face (Sadick et al., 2009). The prescription-only medicine is injected into the muscles underlying the skin causing specific groups of them to become temporarily denervated (Monheit et al., 2007).

THE ROLE OF PEPTIDES AND PROTEINS

These approaches mainly aim at offsetting physical and catabolic processes that exacerbate signs of skin ageing, perhaps the most pragmatic approach to anti-ageing is to modulate cell function such as inducing collagen production by dermal fibroblasts. Gradual loss of collagen production and slackening of elastin is one of the key features of ageing in mature skin. Through the loss of collagen, the skin loses the very vital foundation and building blocks that confer upon it its youthful appearance of fullness, leading to skin thinning, unevenness, and a wrinkled appearance (Draelos, 2008). Therefore, restoration of collagen production is one of the novel ways in which anti-ageing effects may be attained.

The structural protein, collagen, consists of long chains of amino acids strung together to form a triple helix. Its breakdown by the action of collagenase, an enzyme that naturally degrades collagen, leads to the formation of shorter peptide segments composed of 3-5 (or even more) amino acids. It has been suggested that some of these peptide fragments of collagen breakdown may act as signaling messengers arousing the skin to produce more collagen; their presence in the skin acts as an indicator that too much collagen has been broken down which triggers internal repair mechanisms (Draelos, 2008). Thus, a positive collagen balance can be achieved, in one part, from down-regulation of collagenase, leading to decreased collagen destruction and, and in the other, from enhancement of collagen synthesis.

One of the earliest and best-known signaling peptides in cosmetic use today is palmitoyl pentapeptide-3 (Matrixyl, Sederma, France). Matrixyl is composed of Lys (K), Thr (T), Thr (T), Lys (K) and Ser (S), thus the term KTTKS that is sometimes used to refer to the peptide (Draelos, 2008). KTTKS's linkage, through chemical bonding, to the free fatty acid palmitic acid (thus the name Pal-KTTKS), is aimed at improving its ability to penetrate the skin (Draelos, 2008; Bissett, 2009), by conferring upon the peptide a hydrophobic property. Matrixyl contains approximately 800 ppm of Pal-KTTKS and in moisturising cosmeceutical formulations it is applied in concentrations of 1 to 4 ppm. Variations of this peptide have been produced by Croda (www.croda.com). The other signaling peptide is dipeptide-2 (Eyeliss, also made by Croda) which is used in cosmetic applications for reducing "eye bags". Aside from inducing collagen production, other peptides exert their anti-ageing effects through different mechanisms (Gorouhi and Maibach, 2009). Argireline® (Figure 6) is a synthetic neuropeptide (acetyl hexapeptide-3, distributed by Centerchem) which has been reported to demonstrate in vitro blockade of neurotransmitter release from nerves in a botulinum toxin-like fashion (Gorouhi and Maibach, 2009; Blanes-Mira et al., 2002; Choi and Berson, 2006; Lupo, 2005), although it is significantly weaker in strength. Argireline®'s botulinum toxin-like activity is based on blockade of the SNARE (soluble N-

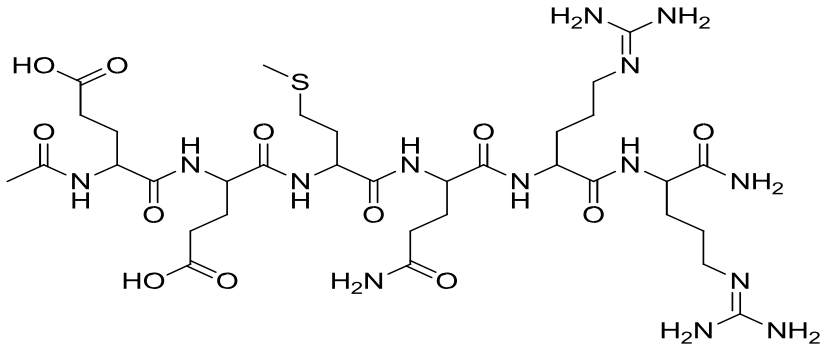

Figure 6. Structure of Argireline®

ethylmaleimide-sensitive factor attachment receptor) protein complex formation, an important step in the Ca2+-dependent synaptic vesicle fusion prior to neurotransmitter release across the synapse (Blanes-Mira et al., 2002). This leads to inhibition of muscular contraction as seen with botulinum toxin; and although it is somewhat less efficacious, Argireline® is also less toxic and non-irritating in comparison to botulinum toxin A. Other peptides have various applications in and are linked to, the induction of dermal cell activity to improve the health of the skin. Serilesine®, for example, is hexapeptide-10 which restores normal activity at the dermal-epithelial junction (DEJ). Its manufacturers (Lipotec, Spain) claim that it improves cell adhesion by enhancing the synthesis of laminin-5, leading to improved contact between skin cells, which results in firmness of the skin. It is also claimed to induce significant increases in the density of the dermis leading to improved skin compactness (Skibska and Perlikowska, 2021). Eyeseryl® is acetyl tetrapeptide-5 which reduces puffy eyes and minimises ring formation under the eyes. It is also reported to inhibit glycation of collagen, thus preventing loss of elasticity and eye bag formation (http://www.lipotec.com/en/products/eyeseryl-reg-peptide/).

Liporeductyl™ is tripeptide-1 which possesses anti-cellulite activity. This effect is achieved via the peptide's lipolytic action acting through inhibition of adipocyte maturation, and its venotonic effect which leads to improved microcirculation (http://www.lipotec.com/en/products/liporeductyl-reg-functional-ingredient/). Both these products are also being distributed on the market by Lubizol Life Science as part of Lipotec™ active ingredients (https://www.lubrizol.com/ Personal-Care accessed on 15 June, 2024). It is important to note that, as with most cosmetic products, scientific evidence to support these marketing claims is not readily available in public literature. The Serilesine® hexapeptide is synthesized from the alpha chain of a laminin isoform, laminin-1, an 850 kDa glycoprotein found in the basal lamina of the DEJ (Skibska and Perlikowska, 2021; http://www.lipotec.com/en/products/eyeseryl-reg-peptide/; http://www.lipotec.com/en/products/liporeductyl-reg-functional-ingredient/; Yoon et al., 2012). Various laminin isoforms exist in various tissues (Ramadhani et al., 2012; Kumagai et al., 2000; Ogawa et al., 2007), of which laminin-1 and laminin-5 are crucial to maintaining the structural integrity of the DEJ, thereby playing key roles in cell proliferation, migration, and adhesion (Lipotec, 2008). Laminin-5 has been found to decrease with age but the use of Serilesine® helps to restore many of the functions including improvement of cell adhesion through stimulation of α6-integrins, improved firmness of skin, increase in dermal density to improve the compactness of skin, and stimulation of formation of hemidesmosomes—cell structures formed by proteins, α6-integrins and laminin-332 (Hopkinson et al., 2014)—which improves cohesion between the dermal and epidermal layers of the skin. These processes help to maintain the structural balance of the skin and are also essential to wound healing (Lipotec, 2008).

Another laminin pentapeptide, YIGSR (tyrosine-isoleucine-glycine-serine-arginine), was identified as a strong enhancer of collagen type-1 synthesis in human dermal fibroblasts (HS27 cells) (Yoon et al., 2012). This effect was shown to occur without any changes in cell proliferation or cellular MMP-1 level, and was mediated via phosphorylation of focal adhesion kinase (FAK) and mitogen/extracellular signal regulated kinase (MEK), since inhibition of these kinases prevented YIGSR-induced collagen-1 synthesis. This suggests that the YIGSR peptide, which corresponds to the 929–933 sequence of the laminin b1 chain (Yoon et al., 2012), may have potential as an active ingredient in anti-ageing cosmetic applications.

A number of related peptides are also being used in the cosmetic industry for unique and varied functions on the human skin. The company Unipex (Quebec, Canada) produces caprooyl tetrapeptide-3 (marketed by LucasMeyer Cosmetics as ChroNOline™) which claims anti-ageing properties (http://lucasmeyercosmetics.com/en/products/product.ph p?id=12&from=name). The peptide is described as a biomimetic lipopeptide derived from a signal peptide that stimulates the production of laminin-5, collagen VII, and fibronectin—key components at the dermo-epithelial junction. The company also

markets Melanostatin®-5 which contains nonapeptide-1, a biomimetic skin-whitening peptide that antagonises α-MSH (alpha-melanocyte-stimulating hormone) receptors involved in melanin production (http:// lucasmeyercosmetics.com/en/ products/product.php?id= 44&from=cat). The α-MSH peptide also exerts anti-inflammatory properties by inhibiting the gene expression of IL-1β and IL-8 proinflammatory cytokines (Capsoni et al., 2015), possibly via inhibition of nuclear factor-kappa B (NF-κB) transcriptional activity (Yang et al., 2015). On the other hand, Kollaren® contains tripeptide-1 which is described as a biomimetic signal peptide, derived from natural growth factor, and is reported to stimulate the production of ECM components (including collagen types I&III, elastin, laminin, and fibronectin), thereby increasing skin firmness and improving healing and tissue renewal (http://www.lucasmeyercosmetics.com/en/products/product.php?id=32&from=cat). Tripeptide-2 (ECM-Protect®) is claimed to provide firmness and improve elasticity of the skin(http://lucasmeyercosmetics.com/en/products/product.php?id=15&from=cat). Cyclopeptide-5 (RonaCare®) from Merck is claimed to reactivate the repair process of aged skin thus stimulating its natural regeneration. Unlike other peptides, cyclopeptide-5 possesses unique stability owing to its cyclic structure and has demonstrated optimal cutaneous efficacy. Finally, a number of patents from Helix BioMedix Inc. claim various bioactivities attributed to peptides of 4 to 6 amino acid residues, including cellular modulation, antimicrobial action, and immunomodulation (Falla et al., 2008; Harris et al., 2011, 2010; Owen, 2002, 2008; Zhang et al., 2008).

Although peptides have been around in the medical field for the past half-century and more, they have only recently been brought into cosmetic usage. Peptides have high biological potencies and are of key value as therapeutic agents despite their relatively low stability. Anti-ageing peptides are categorized as signal peptides, enzyme inhibitor peptides, neurotransmitter-inhibitor peptides, and carrier peptides (Gorouhi and Maibach, 2009). Because of their potential as skin modulating agents, peptides have rapidly emerged on the recent cosmetic scene. They are frequently in formulations accompanied by other active ingredients such as antioxidants, retinoids, and sunscreens. This allows for multiple claims to be made by cosmetic manufacturers with their high cost of production subsequently being transmitted to the consumer in the form of high prices. Peptides may be used to promote cellular growth, immunomodulation or healing of wounds; as synergists or adjuvants to, or in the manufacture of, antimicrobial and anticancer agents. Common side effects of peptides include skin irritation, some individuals develop allergic reactions characterized by redness, swelling, and discomfort.

PLANT STEM CELLS

Stem cells can be obtained from both plants and animals. However, plant sources are preferred due to ethical considerations. Obtaining stem cells from humans and animals can raise ethical concerns (Trehan et al., 2017). Additionally, stem cells from plants do not elicit an immune response, and their acquisition is environmentally friendly and possible for endangered plants as well. Plant stem cells are found in shoot apical meristems and root lateral meristems at the growing tips. These tips contain totipotent cells that can produce any differentiated cell in a plant, enabling it to build new organs throughout its life (Schmid et al., 2008). In cosmetics, plant stem cells are produced using the micro-propagation method with in vitro cell cultures (Barbulova et al., 2014). As active ingredients in cosmetics, plants such as *Oryza sativa* and *Gardenia jasminoides* extend the life of fibroblasts and stimulate their activity; *Symphytum officinale*, *Capsicum annum*, and *Opuntia* species increase the flexibility of the epidermis; *Lotus japonicas* regulates cell division; while *Panax ginseng* rebuilds damaged epidermis (Diana, 2012). The additional uses of these substances include initiating DNA repair in cells that have been exposed to oxidative stress and providing protection against UV radiation. In cosmetic products, they are normally used as lipid-soluble or water-soluble extracts, or as powders, liposomes, nano-emulsions, or suspensions (Barbulova et al., 2014; Georgiev et al., 2018).

BEEVENOMAS AN ACTIVE INGREDIENT IN COSMETICS

Bee venom (BV) and its components are increasingly being used as primary ingredients in various cosmetic formulations including skin creams, balms, face masks, and serums, in Europe. Currently available honey bee venom products include the Manuka® Doctor apinourish range, which contains “Restoring Night Cream” and “Rejuvenating Face Mask” brands. Their other products are apiclear (Skin Balancing Serum) and apirevive (Rub Ease Balm), also marketed as containing purified bee venom, in addition to other ingredients. Other BV based cosmetic products on markets in the UK and EU include: Nectar Balm “Bee Venom Cream” manufactured by Nelson Honey New Zealand and 10 Natural Effects “Bee Venom Essence” manufactured by Laboratorios DIET Esthetic S.A, Spain.

Marketing claims for the BV-based cosmetic products include anti-wrinkle, skin rejuvenating, moisturizing, skin relaxing/warming, skin balancing, and cell metabolism stimulating effects, among others. Given the complexity of the composition of these creams, it may be difficult to attribute any of these effects to a single constituent, given that the actual composition of the purified venom material is a company secret. However, it should be acceptable to believe that the relative success of a cosmetic product on an open free market can be an indicator of the efficacy it affords the user. At the very minimum, these products must be safe to the consumer who may be susceptible to risks of allergic reactions. Thus, allergens have to be identified

and removed; in addition, the end formulation has to be assayed to confirm the absence any unwanted components in the product before being passed for marketing and use.

It should be noted that, apart from cosmetic products, there are also BV based topical pharmaceutical creams both in Europe as well as on the globe. These include Forapin in Germany, Virapin in Slovakia, Apiven in France, Melivenon in Bulgaria, and Apifor in Russia which are used for pain-relieving effects (Matysiak et al., 2011). Although these products have been on the market for quite some time, they have not been available as general-use consumer products for a wide international market. Cosmetics are generally designed to fit the latter purpose but currently available ones have only appeared in the last few years. These products are being marketed as containing “purified bee venom” or “bee venom extracts” (such as 10 Natural Effects Bee Venom Essence by Laboratorios DIET Esthetic S.A.) without further specification. Despite this growing use of bee venom, current literature does not report a sufficient number of studies showing how to assess the composition of cosmetics in general (Gao et al., 2012), let alone the BV content in these products.

The field of formulated BV cosmetics is likely to attract more interest from both manufacturers and consumers in the near future. This is partly due to: (1) the recent development of improved non-destructive BV harvesting technologies that ensure a steady supply of raw material; (2) an increasing proportion of the senior population and the resulting demand for age-defying products and technologies; and (3) the relative success of the existing products—factors which might inspire an influx of other manufacturers. At the same time, BV research maintains widespread mainstream scientific interest for potential applications in cancer therapy, arthritic disorders, and BV immunotherapy (Park et al., 2015; Seppala et al., 2012). The completion of the bee genome sequencing project could raise interest even higher (Nature, 2006; Elsik et al., 2014). These trends point to an anticipated future where BV and related products could become ubiquitous. This could also increase incidences of BV allergic reactions, some of which can be life-threatening. Methods for de-allergenisation of the venom through chromatographic purification before formulation are thus needed.

In addition, screening studies for toxicity and anti-ageing efficacy are necessary to guarantee fit-for-purpose products.

SKIN AND LIFESTYLE

Maintaining youthful skin requires more than just skincare; it also involves a holistic approach that includes a balanced diet, adequate hydration, sufficient sleep, and regular exercise such as 150 min of moderate-intensity activity or 75 min of vigorous aerobic exercise per week for adults (Khan et al., 2023) and a positive mindset. Nutritional status is crucial for healthy skin, as macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and essential minerals) work together to support the skin's barrier functions. Antioxidants from natural foods, particularly those rich in phenolic compounds, protect the skin from oxidative stress caused by exposure to oxygen, UV light, and other harmful agents. Additionally, amino acids are vital for producing the structural proteins and enzymes necessary for the dermal and epidermal layers, contributing to a strong epidermal barrier. Herbal medicines and plant-based oils, such as lavender oil, have also shown promise in promoting wound healing and supporting overall skin health with minimal side effects (Akalın and Selamoglu, 2019).

OTHER INNOVATIONS IN ANTI-AGEING COSMETICS

Cell-based therapies like adipose-derived stem cells (ADSCs) help with tissue regeneration and remodeling by promoting dermal fibroblast proliferation and reducing matrix metalloproteinases (MMPs) (Gentile and Garcovich, 2021). Autologous methods utilize a person's tissue to address skin and soft tissue ageing. These methods include platelet-rich plasma (PRP) for skin rejuvenation, autologous growth factors, fibroblasts, and combinations of dermis, fat, and fascia for generating facial rejuvenation derivatives (Choi et al., 2017). Genetic therapies are being developed to include injectable fillers or topical creams that can moderate alternative splicing. This is a strategy for genetic therapy aimed at remodeling the extracellular matrix, restoring collagen and elastin frameworks, and reversing adipose tissue atrophy (Bramwell and Harries, 2021).

Viral vectors, such as adenovirus, are being used to manipulate growth factors like epidermal growth factors, fibroblast growth factor, keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF), and others in regenerative surgery (Giatsidis et al., 2013). Additionally, epigenetic modifications, such as DNA methylation, are being studied for their potential to reverse ageing (Li et al., 2020). The application of gene therapies has been used to maintain cellular proteostasis (Sabath et al., 2020), a mechanism that prevents skin ageing. Other anti-ageing therapy (Dempsey et al., 2008) and CRISPR/Cas-9 technology (Sabath et al., 2020). Other methods include fat grafting, PRP, and soft tissue fillers. Table 6 shows a summary of the common ageing mechanisms of the skin, anti-ageing approaches, the chemical classes and examples of cosmeceutical ingredients on the market.

CONCLUSION

Cosmetics, including anti-ageing cosmeceuticals, continue to be a key sector for research and development, with growing interest in innovations related to novel ingredients, formulations, and delivery systems. The ideal anti-ageing cosmeceutical formulation should address

Table 6. Comparison of ageing mechanisms, anti-ageing approaches, and the chemical ingredients used.

Ageing mechanism	Anti-ageing mechanism	Chemical class	Examples
Volume depletion in the cutaneous tissues	Reduced trans-epidermal water loss (TEWL)	Occlusive agents	Petrolatum, lanolin
	Improved water adsorption	Humectants	Glycerine, honey
	Formation of a thin film that prevents water loss	Hydrophilic matrices	Proteins, oatmeal bath, hyaluronic acid
Reduced collagen production	Increased collagen synthesis Reduced collagen degradation Stimulation of epidermal cell renewal Anti-oxidant activity	Retinoids	Natural retinoids *(Retinol, retinoic acid and beta-carotene),* Prescription retinoids *(Tretinoin, adapalene)*[£]
	Triggered internal repair mechanisms including more collagen production	Signaling peptides	Palmitoyl pentapeptide-3 (Matrixyl®, Sederma) Dipeptide-2 (Eyeliss®, by Croda)
	Increased collagen synthesis through increased proliferation and migration of human epidermal keratinocyte	Bee venom	Manuka® Doctor products
Free radical-induced cellular, enzymatic, and signaling pathway damage	Scavenging and suppression of reactive oxygen species (ROS)	Anti-oxidants	Plants and their stem cells (Polyphenols, phenolic acids, flavonoids, and peptides)
	Protection of antioxidant defences		Vitamin C, ferulic acid, alpha-lipoic acid, coffee berry, coenzyme Q10
Dermal atrophy and loss of thickness	Increased epidermal thickness, moisture content, dermal collagen production, and dermal perfusion	Alpha hydroxyl acids	Glycolic acid, citric acid, malic acid, and ascorbic acid
Wrinkles in the upper third of the face	Muscle relaxation by inhibition of transmission of impulses	Botox injections	Botulinum toxin A[£]
Flattening of the dermo-epithelial junction, reduction of anchoring fibrils	Blockade of neurotransmitter release from nerves (Botox-like) Restoration of cell adhesion by enhancing the synthesis of laminin-5 Inhibition of glycation of collagen, preventing loss of elasticity and eye bag formation	Peptides and proteins	Argireline® (acetyl hexapeptide-3) Serilesine® (hexapeptide-10) Eyeseryl® (acetyl tetrapeptide-5)
Reduction of fibroblasts and thinning of the epidermis	Extend the life of fibroblasts and stimulate their activity Increase the flexibility of the epidermis Rebuilding damaged epidermis	Plant stem cells	*Oryza sativa, Gardenia jasminoides, Symphytum officinale, Capsicum annum, Opuntia* spp., *Panax ginseng*
UV-light-induced photo-ageing	Decreased UV light exposure of the dermis and deeper layers of the epidermis	Sunscreens or UV filters	Para-aminobenzoic acid (PABA) esters, such as, ethylhexyl dimethyl PABA Salicylic acid derivatives such as, 2-ethylhexyl salicylate Cinnamic acid derivatives such as, isopentyl 4-methoxycinnamate Benzophenone derivatives such as, oxybenzone

Table 6. Contd.

			Dibenzoylmethane derivatives- avobenzone Triazine derivatives such as, ethylhexyl triazone
	Inhibition of matrix metalloproteinases	Cell-based therapies	Adipose-derived stem cells (ADSCs)
	Decreased mRNA expression levels of MMP-1	Peptide nucleic acids	Peptide nucleic acid (PNA) derivative-PNA-20 carboxyethyl fluorene (CEF) (PNA-20 CEF) (Lee et al., 2023)
Upregulation of transcription factor activator protein-1 and induction of matrix metalloproteinases (MMPs)	Inhibition of tyrosinase-related proteins (antimelanogenic) hence lowering UV-induced MMP (Han et al., 2015)	Bee venom	Manuka® Doctor products[¥]
	Inhibition of MMPs production and activity	Plant extracts	Phenolic compounds, flavonoids, alkaloids, uronic and fatty acids
	Reduced matrix metalloproteinase activity leading to tissue regeneration	Retinoids	All-trans retinoic acid and its derivatives, including tazarotene
Decreased oestrogen levels and reduced rates of collagen production	Raising collagen count and increasing skin hydration	Estrogens	Estrogen and proto-estrogens, placental extracts for hair products, etc.[€]

[£]These are prescription drugs; [¥]Several products are available on the market; [€]Safety concerns exist, particularly regarding carcinogenicity.

both intrinsic and extrinsic causes of skin ageing by minimizing damage while enhancing the skin's capacity for regeneration. As such, an effective anti-ageing cosmeceutical formulation should combine ingredients from different chemical regeneration. As such, an effective anti-ageing cosmeceutical formulation should combine ingredients classes to achieve a synergistic effect, but compatibility and safety must remain the top priorities. Efficacy and safety can vary from one individual to another, as different skin types respond differently to cosmetic ingredients. Despite these variations, the field of cosmeceuticals is expected to continue its growth over the next decade. However, it is essential to ensure that products meet the rigorous efficacy and safety standards required by the most stringent markets through scientific validation, including clinical trials, stability, and quality control studies. Strengthening regulatory oversight and enforcement in less regulated markets is crucial to ensure compliance with established safety and efficacy standards, ultimately protecting consumers. Providing consumers with accurate information about product ingredients, benefits, and limitations can empower them to make informed decisions and better manage their skincare needs. Collaboration among industry stakeholders, researchers, healthcare professionals, and regulatory agencies will foster knowledge sharing, innovation, and best practices within the anti-ageing cosmetic industry.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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