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Review article

Anti-aging peptides for advanced skincare: Focus on nanodelivery systems

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A B S T R A C T

Skin plays an essential role in our personal image and aesthetics as it is where the first signs of aging are visible. As a way to prevent and mitigate this natural physiological process and achieve a more youthful appearance, consumers are constantly looking for innovative options of anti-aging skincare products, including more effective and safer ingredients. Particularly, peptides are cosmetic ingredients present in anti-aging skincare formulations attending to their efficacy in reducing wrinkles and hyperpigmentation, and/or stimulating collagen production. Moreover, peptides are less irritating alternatives regarding conventional cosmetic ingredients against skin aging. However, despite these advantages, peptides have considerable difficulty to penetrate the *stratum corneum*, which hinders their bioactivity. This occurs attending to their high molecular weight, hydrophilic character, and high susceptibility to enzymatic degradation, requiring the application of formulation technologies to improve the stability and the release pattern of peptides through the skin. A detailed exposition focused on smart and multifunctional nanodelivery systems that have been used to encapsulate peptides on anti-aging skincare formulations is provided, within the scope of research and development for anti-aging skincare products. Briefly, it is demonstrated that these biomolecules are a reliable and outstanding alternative considering retinoids and sunscreens against skin aging.

1. Introduction

Having well-groomed and healthy skin is a trend pursued by most consumers nowadays [1], therefore, to prevent and reverse signs of aging and achieve a youthful appearance, women and men turn to cosmetics. The increasing demand for these products, particularly anti-aging formulations, requires from the cosmetic industry not only more research in the field of skin aging but also the development of new formulas, with innovative and effective cosmetic ingredients to achieve consumer requirements [2].

Peptides, are cosmetic ingredients, broadly applied to the skin to achieve a local effect, however, these molecules face a significant obstacle to their action, the skin barrier [3]. In fact, skin is an effective

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Abbreviations

AA	L-ascorbic acid
AMP	Antimicrobial peptide
Cu-GHK	Copper tripeptide-1
Da	Dalton
DPPH	2,2-diphenyl-1-picrylhydrazyl
EA	Edge activators
ECM	Extracellular matrix
IL-6	Interleukin-6
MMP	Metalloprotease
Pal	Palmitoyl
Pal-KVK	Palmitoyl tripeptide-5
Pal-KVK-AA	Conjugation of pal-KVK with L-ascorbic acid
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
SNAP-25	Synaptosomal-associated protein of 25 kDa
SNARE	Soluble N-ethylmaleimide-sensitive-factor attachment protein receptor
TEWL	Transepidermal water loss
TGF	Transforming grow factor
UV	Ultraviolet

barrier against external molecules which is, primarily, due to the stratum corneum, a resistant layer formed by corneocytes, surrounded by an intercellular cement composed by lipids (ceramides, free fatty acids and cholesterol) [4], that prevent both the exit of important constituents such as water, minerals, and proteins, and the entry of potential aggressors [3]. In addition to the lipophilicity and abrasion resistance provided by this layer, the skin still has a multilayer structure and active enzymes [5], which makes the barrier even more efficient [6].

Thus, permeation of peptides is a difficult task [7], then for them to effectively penetrate through the skin and ensure the desired effect, it is advisable they meet some ideal physical-chemical properties: molecular weight below 500 Da, log of partition coefficient between 1 and 3 and good aqueous solubility. Nonetheless, anti-aging peptides, generally, have a molecular weight of over 500 Da, low lipid permeability (partition coefficient <1) and are also substrates for various proteolytic enzymes in the skin, which are responsible for their premature degradation and prevent them from reaching the dermis in adequate concentrations. Despite this, peptides seem to be able to overcome this difficulty since they can be modified several times through the substitution and alteration of amino acids, which constitutes an advantage regarding other cosmetic ingredients, in terms of production cost, toxicity, solubility, potency, formulation, and skin penetration [8].

Chemical modification of peptides allows through conjugation with hydrophobic chains, to form more lipophilic conjugated peptides, such as palmitoyl tripeptide-1, palmitoyl tetrapeptide-7 and palmitoyl tripeptide-5 [9] to ensure its penetration in the skin [10]. Beyond chemical modification, there are other techniques that can be applied to peptides, e.g., physical techniques, including iontophoresis and microneedles, which are used with the aim of temporarily and reversibly modify the skin barrier, allowing the penetration of low lipophilic or neutral peptides, such as acetyl hexapeptide-3 through the *stratum corneum* [9] and nanodelivery systems, which constitute a very useful technology, providing the transport of peptides [11], such as palmitoyl tripeptide-5 [12], improving their stability, protecting them from degradation and enhancing their permeability [13], which allows a more efficient and targeted delivery through the skin.

With the employment of the aforementioned approaches, it is possible to overcome the major drawbacks of peptides, enhancing their performance and delivery. Such scenario makes them viable alternatives over proteins, which in their native form (e.g., collagen) can cause skin irritation and allergenicity [8], and have a higher molecular weight (approximately 300 KDa), which makes them more difficult to be applied in water-based cosmetics [14]. Therein, peptides have been broadly used by the cosmetic industry, thanks to their high safety profile [15], wide applicability, multifunctionality on the skin, and the possibility of conjugation with other cosmetic ingredients. More specifically, several peptides can penetrate the top layer of the skin and act as accelerators, triggering specific functions such as collagen support to obtain a firmer skin; block neurotransmitter signals, to prevent skin muscle hyperkinesis and obtain more relaxed skin; regulate fibroblasts to prevent the degradation of matrix proteins and also include antioxidant and antimicrobial activity, which makes them great allies against skin aging [9].

Throughout this manuscript, the main anti-aging peptides described in the literature until this date will be addressed, as well as their mechanisms of action, effects on the skin, potential studies that support their effectiveness in combating skin aging, and innovative strategies that improve their permeation through the skin.

2. Skin aging and conventional anti-aging active ingredients

Aging is a multifactorial and complex biological process that affects all organs of the human body. Skin, as a covering and protective organ, is no exception, so it also suffers the action of aging, which is characterized by the erosion of its structure, reduction of its functionality and ability to regenerate. The aging process comprises several changes, concerning to homeostasis, structure, function, and appearance. Intrinsic aging, on one hand, is an endogenous and physiological process, responsible for the natural aging of cells and is, mostly, due to genetic factors, but also to hormonal imbalances, such as the decrease of estrogen production during menopause. This type of aging manifests itself slowly as age advances and with the exception of hormone supplementation, the possible interventions to counteract this process are complex [16].

Thereby, extrinsic aging is the main focus of study. This process is a consequence of external factors to the human body, namely pollution, diet, smoking, alcohol consumption, repetitive muscle movements, exposure to sunlight, among others [16]. These factors stimulate the natural aging of the cells and, among them, ultraviolet (UV) radiation is a key factor, since it is responsible for and clinical changes in the skin, i.e., photoaging [17]. Photoaging results from repeated and unprotected sun exposure, which culminates in the premature aging of more exposed body areas, such as the neck, hands, and face. This phenomenon is mainly due to the action of UVA radiation, which given its longer wavelength, penetrates more deeply into the skin, reaching the dermis, so it can damage its connective tissue and increase the risk of skin cancer [18].

With the combination of these two aging processes, synergistic effects occur in the skin, culminating in a more aged appearance, rough and dry texture, appearance of wrinkles, changes in pigmentation, loss of firmness and elasticity, and reduced barrier integrity [19]. Therefore, for the consumers achieve "successful aging", minimizing as many as possible signs of aging on the face and body skin, they can change habits and lifestyle, use of invasive procedures (radiofrequency, chemical peeling, intense pulsed light, botulinum toxin A injection), medication (hormone replacement therapy), and cosmetic care [20]. Cosmetic care comprises daily skincare, sun protection (appropriate to the consumer's skin type), and the application of topical anti-aging products [21].

The anti-aging formulations aim to act on two main components of the skin, collagen, and elastin - widely affected during skin aging - to avoid their degradation, and to ensure the prevention and reduction of wrinkles, loss of firmness, and hyperpigmentation among other undesirable effects [22], without having to resort to invasive procedures.

Several compounds are considered active in combating skin aging and can be included in formulations for topical use, among which (see Table 1): UV filters, that can act in two ways: blocking UV radiation (inorganic/physical blockers) or absorbing UV radiation and releasing it

Table 1
Conventional active ingredients used in topical anti-aging formulations.

Classification		Ingredients	Ref.
Antioxidants		Vitamin C	[26]
		Vitamin B_3	[27]
		Vitamin E	[28]
		Ubiquinone	[29]
UV filters	**Organic/ Chemical**	Avobenzones	[30,
		Oxibenzones	31]
		Menthyl anthranilate	[32]
		Diethylamino hydroxybenzoyl	[33]
		hexyl benzoate	[34]
		Para-aminobenzoic acid	[35]
		Cinnamates	
		Salicylates	
		Camphor derivative	
	Inorganics/ Minerals	Zinc oxide	[30]
		Titanium dioxide	[36]
		Iron oxide	
Moisturizers	**Humectants**	Glycerin	[37]
		Urea	[38]
		Honey	
		Panthenol	
	Emollients	Octyldodecanol	[37]
		Dimethicone	[38]
	Occlusive agents	Paraffin	[37]
		Lanolin	[38,
		Petrolatum	39]
Retinoids		Retinoic acid (Tretinoin)	[40]
		Retinol	[41]
		Retinaldehyde	

in the form of energy (chemical/organic absorbers, which are crucial against skin cancer and premature skin aging, caused by UV radiation [23]; retinoids, derivatives of vitamin A relevant for epidermal turnover, since retinoids stimulate the differentiation of keratinocytes, as well as cell renewal [24]; antioxidants, such as vitamin C and B_3, which prevent the formation of ROS induced particularly by UV radiation, thus reducing skin damage and preventing collagen impairment [22]; and moisturizers that improve water retention at the stratum corneum, often lost during the skin aging [25].

3. Anti-aging peptides

Anti-aging peptides are applied to the skin to obtain a local effect [9], acting on the factors that cause changes in the structure, appearance, functionality, and homeostasis of the skin. According to their mechanism of action, anti-aging peptides can be categorized as bioactive peptides, which act on the skin repair and renewal systems [42], stimulate collagen synthesis, cell proliferation, and reduce melanogenesis [43]; antioxidant peptides, capable of eliminating ROS from the body [44] and antimicrobial peptides (AMPs) that are involved in the maintenance of a healthy skin microbiome.

Despite its beneficial effects, these peptides are hydrophilic substances, thus may have difficulty crossing the epidermal barrier, so conjugation with fatty acids, such as palmitic acid, is frequently used to increase protection of the peptides against enzymatic action, and their lipophilic character improve delivery through the skin [45,46].

Anti-aging peptides are therefore appealing ingredients for the cosmetic industry because of their wide applicability and also owing to their higher safety profile [2], which will be analyzed below.

3.1. Bioactive peptides

Bioactive peptides are molecules consisting of 2–20 amino acids [47], that participate in numerous biochemical pathways essential for the proper functioning of the human body [48]. Additionally, they have a broad spectrum of biological action, concerning inflammation, wound healing, stimulation of cells to produce extracellular matrix (ECM) proteins, among others, and their activity depends on the amino acids and their sequence.

The cosmetic industry, in particular, seems to attribute great value to these cosmetic ingredients that, thanks to their broad applications are strong allies in the fight against skin aging [2].

Regarding bioactive peptides used in cosmetics, 4 classes can be distinguished based on their mechanism of action: signal peptides that act as messengers to stimulate the production of ECM proteins and prevent their degradation; carrier peptides, which transport elements associated with enzymatic processes, such as copper [49]; neurotransmitter inhibitor peptides, that prevent the release of acetylcholine at the neuromuscular junction, providing a botox-like effect; and enzyme-inhibiting peptides, which reduce the activity of enzymes involved in skin aging.

3.1.1. Signal peptides

Signal peptides or collagen-stimulating peptides are responsible for stimulating the production of ECM proteins, reduce the degradation of existing skin collagen and promote cell growth and migration. Therefore, currently, signal peptides are widely used as active ingredients in anti-aging products [8], to restore collagen levels related to the senescence of fibroblasts, which proliferate more slowly and consequently decrease collagen synthesis (particularly type 1), as well as further degradation by proteolytic enzymes, with the aim of obtaining a more elastic, firm and smoother skin [50]. This is possible since they act as messengers that modulate the protein turnover of the skin [2], i.e., they have the ability to resemble the transmitted signal during the synthesis of ECM proteins, which leads to increased fibroblast activity, with consequent production of collagen and elastin [8,49,50].

Moreover, these peptides have other metabolic functions, so they can act as growth factors. This is the case of Hexapeptide-12 [51], a signal peptide that is able to activate protein kinase C, which is the main responsible for cell growth and migration.

Diverse signal peptides are available for topical application (see the selected examples in Table 2), which will be display beneath.

3.1.1.1. Palmitoyl tripeptide-1. Palmitoyl tripeptide-1 is a signal peptide that results of the conjugation of palmitic acid with tripeptide-1which performs two functions: signal peptide and carrier peptide when complexed with copper (II) [50]. Palmitoyl tripeptide-1 act on the TGF-β, which is responsible for stimulating dermal fibroblasts to produce ECM proteins, which will reinforce the epidermis, but also reduce wrinkles [52].

Among the anti-aging products available on the market that contain this peptide, exist two serums developed by Sederma: Biopeptide CL™, which contains only palmitoyl tripeptide-1, and Matrixyl™ 3000, which combines palmitoyl tripeptide-1 with palmitoyl tetrapeptide-7 [51,53]. Biopeptide CL™ has comparable activity to retinoids, since like them it stimulates the production of ECM proteins [2,49], however, does not induce skin irritation.

Additionally, to evaluate the efficacy of Matrixyl™ 3000 [54], a study was performed on 24 volunteers who applied a cream containing this cosmetic ingredient and also a placebo cream on each half of the face twice a day for 2 months. After 56 days of use, Matrixyl™ 3000 decreased the roughness (14.0 %), reduced the deep wrinkle area (44.0 %) and their density (37.0 %), providing improvement of the skin tone (15.0 %) as well elasticity [51].

3.1.1.2. Palmitoyl tripeptide-5. These signal peptide results from the conjugation of tripeptide-5, with a palmitoyl moiety in the N-terminal portion (Pal-KVK). Pal-KVK is a patented peptide under the trade name SYN®-COLL and is one of the most common signal peptides in cosmetic formulations for sensitive skin. Similarly, to palmitoyl tripeptide-1, this signal peptide seems to act at the level of the TGF-β factor, allowing an improvement in skin firmness and elasticity [2]. Another possible

Table 2
Selected examples of anti-aging peptides: summary of their characteristics and observed effects in the skin.

INCI designation	Commercial name	Production	Molecular target	Mechanism of action	Skin effects	Ref
Palmitoyl tripeptide-1	Biopeptide CL™	Chemical synthesis	TGF	Synthesis of ECM proteins and glycosaminoglycans	↑ Skin thickness ↑ Skin texture ↓ Wrinkle ↑ ECM synthesis Non-irritating Non-sensitizer	[104] [51] [105, 106]
Palmitoyl tripeptide-5	SYN®-COLL	N/A	TGF /Tyrosinase	TGF stimulation and reduction of tyrosinase activity	↓ Pigmentation ↑ Skin firmness ↑ Skin elasticity ↓ Skin roughness	[2] [56]
Palmitoyl hexapeptide-12	Biopeptide EL™	Chemical synthesis	IL-6	Reduce IL-6 production	↑ Skin firmness ↑ Skin tone ↑ Skin elasticity ↓ Skin irritation	[51] [59]
Copper tripeptide-1	N/A	Chemical synthesis	Copper	Copper transport for collagen, elastin, proteoglycans and glycosaminoglycans synthesis	↑ Keratinocyte proliferation ↑ Collagen synthesis ↑ Skin firmness ↑ Skin elasticity ↑ Wound healing ↓ Wrinkles	[2] [51] [52] [107] [108]
Manganese tripeptide −1	N/A	N/A	Manganese	Cofactor of manganese-superoxide dismutase	↓ Photodamage ↓ Pigmentation ↓ Skin roughness	[51] [63]
Soy peptide	N/A	Complex mixtures of peptides obtained by protein hydrolysis	MMPs	Inhibition of MMPs	↑ Collagen synthesis ↑ Elastin synthesis ↑ Fibronectin synthesis	[109]
Silk fibroin peptide	N/A	Complex mixtures of peptides obtained by protein hydrolysis	Tyrosinase	Inhibition of tyrosinase	↓ Melanin synthesis	[8] [50]
Hydrolyzed rice bran protein	N/A	Complex mixtures of peptides obtained by protein hydrolysis	Tyrosinase	Inhibition of tyrosinase	↑ Melanogenesis inhibition ↑ Skin elasticity ↓ TEWL ↓ Skin irritation	[110]
Acetyl hexapeptide-3	Argireline	Chemical synthesis	SNARE	Inhibition of the SNARE	↑ Skin firmness ↑ Skin tone ↓ Wrinkles	[2] [50] [68] [69]
Pentapeptide-3	Leuphasyl®	N/A	Opioid receptors (coupled to inhibitory G proteins)	Inhibition of acetylcholine release	↓ Wrinkle size ↑ Skin roughness	[73]
Acetyl octapeptide-3	SNAP-8	N/A	SNARE	Inhibition of the SNARE	↓ Wrinkles	[70] [74]
Glutathione	N/A	Chemical synthesis	Tyrosinase	Inhibition of tyrosinase	↓ Pigmentation ↓ Wrinkles ↓ ROS production	[84] [111]
Hydrolyzed collagen peptides	N/A	Complex mixtures of peptides obtained by protein hydrolysis	N/A	N/A	↑ Antioxidant activity	[14] [80] [112]

Abbreviations: **ECM** - Extracellular matrix, **IL** - Interleukins, **MMP** - Metalloprotease; **N/A** - Not available; **ROS** - Reactive oxygen species; **SNARE** - N-ethylmaleimide-sensitive factor activating receptor; **TEWL** - Transepidermal water loss; **TGF** - Transforming growth factor.

mechanism of action of Pal-KVK is the inhibition of melanin production by reducing the activity of tyrosinase, that catalyzes the oxidative polymerization of tyrosine to melanin [55].

A study has been performed by Kim et al. [56] to evaluate the anti-wrinkle effect of a signal peptide resulting from the conjugation of Pal-KVK with L-ascorbic acid (Pal-KVK-AA). In this study, 21 healthy Korean women aged between 41 and 55 years applied on half of their faces for 12 weeks (twice a day) a cream containing 0.75 mg/mL Pal-KVK-AA and the other half a placebo cream (without Pal-KVK-AA) under the same conditions. After 12 weeks, the results indicated that the cream containing 0.75 mg/mL Pal-KVK-AA reduced skin roughness (about 10.0 % reduction regarding placebo group) and enhanced dermal density regarding the application of placebo cream. Additionally, it was performed an *in vitro* study, in which human neonatal dermal fibroblasts were subjected to various concentrations of Pal-KVK-AA (0.1; 0.5; 1; 2 and 4 μg/mL). The results showed that at a concentration of 4 μg/mL Pal-KVK-AA, the expression of procollagen 1 was close to 200.0 %, compared to 150.0 % in the positive control (TGF-β, 0.01 μg/mL).

3.1.1.3. Palmitoyl hexapeptide-12. Palmitoyl hexapeptide-12 is a signal peptide that reduce the production of interleukin-6 (IL-6) by keratinocytes and fibroblasts. IL-6 is a pro-inflammatory cytokine that regulates inflammation response [57], and in a normal situation, it remains at low levels, nevertheless, during a potential aggression or damage (e.g. UV radiation exposure) it is released rapidly [50], in order to attract immune cells to the site of injury and infection and allow skin repair. Although immune cells have a crucial intervention, ROS are released during their action, which stimulate the secretion of metalloproteases

(MMPs) culminating in faster degradation of the skin matrix [58]. Thus, by reducing IL-6 production, it is thought that palmitoyl hexapeptide-12 may decrease skin matrix degradation, common during skin aging.

A study was conducted to evaluate the efficacy of palmitoyl hexapeptide-12 in skin aging. In this study 10 female volunteers (32–56 years old) applied a cream containing 0.0004 % (w/w) palmitoyl hexapeptide-12 on the forearm, and the placebo in the contra-lateral arm, twice daily, for one month. The results of this study showed that this peptide enhanced skin firmness by 20.0 % and increased skin tone by 33.0 % considering placebo group [59].

3.1.2. Carrier peptides

These are amino acid sequences responsible for the stabilization, transport, and delivery of trace elements to epithelial skin cells [2]. One of the trace elements carried by this class of peptides is copper (II), which is essential for the human body, as it is a cofactor for enzymes such as superoxide dismutase, a metalloenzyme responsible for the elimination of free radicals [60] and lysyl oxidase, involved in the covalent cross-linking of the fibers of collagen and elastin. Therefore, it plays an important role in improving the appearance and texture of the skin.

3.1.2.1. Copper tripeptide. Copper tripeptide-1 (Cu-GHK) was the first peptide used in cosmetics for skin application, and resemble the alpha chain of collagen [50].

This carrier peptide is very versatile concerning several skin functions, including stimulation of collagen, glycosaminoglycans [52], elastin and proteoglycans synthesis by fibroblasts [57], as well as anti-inflammatory response. Cu-GHK comprises numerous cosmetic applications, being used in products for its efficacy in reducing wrinkles, hyperpigmentation and photodamage, in stimulating keratinocyte proliferation and improving the skin barrier [50].

A study conducted by Huang et al. [61], demonstrated that Cu-GHK when used with therapeutic light-emitting diode (light therapy to prevent aging and aid the healing process) led to an increase in procollagen type I synthesis (about 230.0 %), as well as in basic fibroblast growth factor production (about 30.0 %). Therefore, it is concluded that Cu-GHK may be an ally in combating skin aging, since it promotes fibroblast growth and collagen synthesis, as well as epidermal repair.

3.1.2.2. Manganese tripeptide-1. Manganese tripeptide-1 is a carrier peptide of manganese, a crucial metal for the functioning of manganese-superoxide dismutase, enzyme that neutralizes free radicals induced by UV radiation [62], and responsible for skin degradation and its premature aging, which consequently contributes to the antioxidant and protective effect on the skin.

Hussain et al. [63] investigated the effects of a facial serum containing manganese tripeptide-1, on facial skin photoaging. In their study 15 female participants, aged 40–70 years, who had moderate facial damage and hyperpigmentation, applied the test serum for 12 weeks in the face and neck twice daily. During the study, the researchers evaluated the photodamage, according to a numerical scale from 0 to 4 (0-none, 1-minimal, 2-mild, 3-moderate, 4-severe), in order to evaluate the results obtained by using the manganese-tripeptide-1 based serum (post-treatment) and compare them to the pre-treatment. After 12 weeks of use, benefits were observed on the skin, namely on hyperpigmentation (score higher than 3 pre-treatment and lower than 2.5 post-treatment), skin roughness (score 2.5 pre-treatment and lower than 1.5 post-treatment), solar lentigines (score higher than 2.5 pre-treatment an lower than 2 pos-treatment), sallowness (2.5 in pre-treatment and lower than 1.5 pos-treatment) and fine wrinkles (close to 3 in pre-treatment and close to 2.5 pos-treatment). Therein, through the results, it was possible to conclude that the serum reduces the effects of skin photoaging, enhancing its texture and appearance.

3.1.3. Enzyme-inhibiting peptides

Enzyme inhibiting peptides work by reducing the activity of enzymes that contribute to skin aging, particularly MMPs. With the accumulation of ROS from light exposure, there is an increase in the synthesis of MMPs, which leads to an excessive degradation of ECM proteins and consequently the loss of skin elasticity and firmness [64]. Therein, silk fibroin peptides and rice peptides may constitute viable alternatives in combating skin aging.

Considering this group, serpin A1-III is a decapeptide commercially identified as KP1, produced by chemical synthesis from the C-terminal portion of serpin A1, a serine protease inhibitor that acts as a potent neutrophil elastase inhibitor, which promotes the deterioration of ECM components. Serpin A1-III possess potential anti-aging properties as induce a considerable increase in type I collagen levels [2].

Silk fibroin peptides are molecules extracted from silkworm cocoon and are generally composed of glycine (major component), alanine, serine and tyrosine [65]. These peptides are biologically compatible, which is thought to be due to their structure, consisting of intercalated hydrophilic and hydrophobic domains [66], that may facilitate their interaction with biological structures, in particular, the phospholipid bilayer of the skin. Furthermore, silk fibroin peptides seem to inhibit tyrosinase, and may constitute an appealing cosmetic ingredient for use in anti-aging formulations.

Finally, rice peptides are obtained through the processing of rice proteins which possess low molecular weight and potential applications in skin aging. To evaluate the antioxidant and enzyme inhibitory activity of rice protein hydrolysates (rice peptides), a study was performed by Chen et al. [67]. The results of the study showed that these peptides have antioxidant activity, which is related to the amino acids present in their structure (e.g. cystein possess antioxidant properties). Also, this peptide was responsible for 50.0 % inhibition of the activity of hyaluronidase (8.91 mg/mL) and tyrosinase (107.6 mg/mL), which are enzymes involved in the process of skin aging.

3.1.4. Neurotransmitter inhibitor peptides

Neurotransmitter inhibitor peptides are molecules that mimic the action of botulinum neurotoxin A [53], inhibiting the release of acetylcholine, the major player in muscle contraction process, in which large compressive tensions occur, leading to the formation of fine lines and wrinkles, whose shape and depth correlate with the level of contraction. Acetyl hexapeptide-3, trade name Argireline®, is one of the best studied neurotransmitter inhibitor peptides [49,68]. This peptide is a peptide fragment of SNAP-25 protein [69,70] a membrane protein that mediates a cascade reaction, in which, acetylcholine vesicles fuse with the membrane [2]. Therefore, this peptide competes with SNAP-25 for the binding site in the SNARE complex, leading to destabilization of its structure, which prevents the release of acetylcholine at the nerve endings, and culminates in inhibition of muscle cell contraction, producing muscle relaxation, smoothing wrinkles and fine lines, which allows enhanced skin firmness and tone [50]. Additionally, it presents anti-wrinkle activity, and less toxic potential than botulinum neurotoxins widely applied [71], so they constitute an alternative in anti-aging products. Wang et al. [68] developed a study to evaluate the anti-aging potential of this peptide, wherein 60 Chinese volunteers applied for a period of 4 weeks (in the periorbital region) an emulsion containing 10.0 % acetyl hexapeptide-3 or a placebo emulsion (without acetyl hexapeptide-3). The results of the study showed that acetyl hexapeptide-3 has an anti-wrinkle efficacy of 48.9 % compared to placebo (0.0 %).

Another peptide with anti-aging potential is pentapeptide-3, trade name Leuphasyl®, that mimics enkephalins mechanism. Enkephalins are endogenous opioid pentapeptides that inhibit the release of acetylcholine because these pentapeptides interact with opioid receptors, which are coupled to inhibitory G proteins. Once bound to these receptors, the G-protein subunits are released, inhibiting the release of acetylcholine and consequently avoiding muscle contraction and preventing skin aging [72]. In this regard, it was executed a study to analyze the anti-wrinkle effect of Leuphasyl®. Thus, 14 volunteers, with ages between 39 and 64 years, applied around the eyes a cream containing 5.0 % Leuphasyl® twice a day for 28 days. By taking silicone impressions of the wrinkles around the eyes of the volunteers, it was detected an 11.6 % reduction in wrinkles on day 28 versus day zero [73].

Moreover, acetyl octapeptide-3, trade name SNAP-8 is an acetylcholine release inhibiting peptide produced from the structure of acetyl hexapeptide-3 by adding a chain consisting of 2 amino acids (alanine and aspartame) [70]. Therefore, like acetyl hexapeptide-3, it is responsible for destabilizing the SNARE complex (it competes with SNAP-25), which prevents the release of acetylcholine and consequently, the muscle contraction responsible for the appearance of wrinkles [2]. On this subject, it was conducted an *in vivo* study to evaluate the efficacy of a cream containing 10.0 % acetyl octapeptide-3. During the study, 17 female volunteers applied this cream to the peri-orbital region for 28 days. After this period and through silicone impressions it was verified a 63.0 % reduction in wrinkle depth [74].

Recently, it was also developed a biomimetic endorphin peptide functionalized in a delivery system complex based on conjugated linoleic acid amidified with glutathione, called Peptilift. This botox-like peptide demonstrated wrinkle reduction (55.0 %); increased skin elasticity (49.0 %); and promoted skin revitalization.

3.2. Antioxidant peptides

Skin aging is largely due to the accumulation of oxidative damage, resulting from the insufficient bioavailability of antioxidants regarding the increased amount of ROS produced, by the mitochondrial aerobic metabolism or solar UV radiation [75]. Consequently, ROS accumulate and activate several signaling pathways, responsible for the reduction of collagen synthesis; production and activation of MMP and release of the senescence-associated secretory phenotype (SASP) [76]. Studies with Tel-E6E7 human stem cells suggested that ROS induced by UV radiation, promote MMP-1 activity in keratinocytes and fibroblasts of the dermis [77]. Thereby, to prevent oxidative stress, antioxidant peptides are used owing to their ability to transfer an electron or hydrogen atom to stabilize radicals, or to their capability to complex ions, such as copper, essential for the functioning of enzymes involved in the inflammation and aging process, inhibiting them. Moreover, antioxidant activity is still dependent on their molecular weight, as low molecular weight peptides have a greater ability to donate hydrogen or electrons; their hydrophobicity that improve the accessibility to hydrophobic cellular targets, e.g. biological membranes; and their amino acid sequence [14].

Hydrolyzed collagen or collagen peptides results from the denaturation of collagen protein by enzymatic hydrolysis. In the cosmetic industry, hydrolyzed collagen is widely used [42], owing to their biocompatibility [78], easy biodegradability, and very low toxicity when topically applied [79]. Hydrolyzed collagen has been identified as a good moisturizer for the stratum corneum of the epidermis, though, as far as its anti-aging benefits, its mechanism of action is not fully identified [14].

The antioxidant activity of peptides is related to its molecular weight, thus smaller peptides up to 10 KDa (equivalent to 2 to 10 amino acids) show higher antioxidant activity.

To assess the relationship between the molecular weight of collagen hydrolysates from sheep skin (which is dependent on the time of hydrolysis of the collagen) and its antioxidant activity, Léon-Lopez et al. [80] conducted a study in which two free radicals were used: ABTS (suitable to evaluate hydrophilic and hydrophobic antioxidants) and DPPH. The results of the study showed that the highest radical scavenging activity was seen after 4 h of hydrolysis of the collagen protein, 67.6 % for ABTS and 52.75 % for DPPH. Thus, collagen hydrolysates of small size and composition in antioxidant amino acids e.g., glutamic acid (due to the high hydrolysis time), guarantee a considerable antioxidant activity, and may be valid options in combating skin aging caused by oxidative stress.

3.2.1. Glutathione

Melanin, a natural protective pigment of the skin, have two mechanisms of action: acts as a physical barrier and absorption filter, which disperses and limits the penetration of UV radiation, and as an antioxidant, eliminating harmful free radicals from the skin [81]. However, the accumulation of ROS from UV radiation activates the enzyme tyrosinase involved in the melanogenesis process, leading to an overproduction of melanin, which causes undesirable hyperpigmentation of the skin [44]. Therefore, there is considerable demand for skin-whitening agents. Glutathione is a low molecular weight thiol-tripeptide, that presents a powerful antioxidant [82] and anti-melanogenic activity [83], since eliminates free radicals, such as peroxides, which are responsible for tyrosinase activation, and chelates through its thiol group, the copper necessary for the functioning of the enzyme tyrosinase, which leads to its inhibition.

A recent study carried out by Tsay et al. [84], assess the photoprotective effect of three antioxidant substances, glutathione, ergothioneine and ferulic acid. For this purpose, human fibroblasts were exposed to UVB radiation (280–360 nm) and subsequently subjected to different concentrations of each antioxidant: Ergothioneine (1 μM and 50 μM), ferulic acid (10 μM, 50 μM and 100 μM) and glutathione (10 μM, 50 μM and 100 μM). The results of the study demonstrated the highest % of ROS inhibition achieved by each of the oxidants was 109.5 %, for the 1 μM ergothioneine concentration, 151.6 % for 100 μM ferulic acid and 112.8 % for 100 μM glutathione. However, the mixture of 2 oxidants, particularly, ferulic acid at 100 μM + glutathione at 100 μM and ferulic acid 50 μM + glutathione at 50 μM, have the greatest photoprotective effect. Therefore, glutathione seems to be a potent antioxidant ingredient to protect against photoaging.

3.3. Antimicrobial peptides

The skin has a balance between microorganisms residing on its surface, which are essential for the homeostasis of the epidermal barrier and once disturbed it can be associated with various skin disorders (reducing the acidity of the skin) [85,86]. Similarly, recent data has associated skin aging process with microbial imbalance [19,87]. Thus, to evaluate this hypothesis, a study was conducted by Kim et al. [88], for the assessment of the differences present between young and mature skin. For this purpose, the skin of 73 healthy women belonging to different age groups (25–35 years and 56–63 years) was analyzed. Through this study it was possible to observe differences regarding indicators of skin aging, namely transepidermal water loss (TEWL higher in older women) and sebum production (reduced in older women), as well as changes in the skin microbiome. While Proteobacteria and Actinobacteria were more abundant in older skin, Bacteroidetes and Firmicutes were more prevalent in young skin. Such changes seem to suggest that modifications in the skin microbiome, can be associated to skin aging [87].

AMPs are polypeptides, composed of 10–100 amino acids, that play an important role in skin immunity since they are responsible for the elimination of pathogenic microorganisms, being an important line of defense against microbial colonization [89]. Chung et al. prepared a study to evaluate the antimicrobial activity of a synthetic antimicrobial peptide (based on a peptide derived from Komodo dragon histone H1) against the bacteria *P. aeruginosa* and *S. aureus*, as well as to analyze its ability to promote the migration of keratinocytes. For this purpose, an EC_{50} assay, in mouse wound model, was performed, in which, for the concentration range (0.50–4.62 μM), this peptide showed effective antimicrobial activity against both bacteria. On the other hand, through a wound closure trial by scraping, it was found that in the interval of 7–14 h, this peptide increased migration of keratinocytes to the wound area (compared to the control), which conduct to improved epidermal barrier repair and consequent wound healing [90]. Another study was conducted in order to analyze not only the antimicrobial activity of the peptide Tilapia Piscidin 4 but also its contribution to wound healing. In this study skin wounds were contaminated with methicillin-resistant *S. aureus* and their evolution until they closed was compared. After the study, the wounds treated with Tilapia Piscidin 4, did not have an initial expansion as occurred with untreated wounds or wounds treated with methacycline or vancomycin. In addition, wounds treated with Tilapia Piscidin 4 closed more quickly (day 21) than wounds treated with vancomycin (day 27), which encourages its activity in skin renewal and repair [91].

Defensins, in particular, are cationic AMPs with a broad spectrum of action, since they have activity against viruses and bacteria [10]. Divided in α- and β-defensins, they participate in the immune response and appear to be able to improve skin structure and appearance, through an additional mechanism of action, the stimulation of multipotent stem cells [92]. Multipotent stem cells are cells capable of self-renewal and can also give rise to other cell types. These are subdivided into several types, among which, the LGR6-positive stem cells that play an important role in skin renewal. LGR6-positive cells are located above the bulb of the hair follicle (see Fig. 1) and are responsible for the maintenance of the sebum-producing glands and epidermis [93]. The epidermis repair is achieved through the activation of these cells by defensins during the wound healing process, which ensures the production of new basal cells that can replace the degraded keratinocytes [94] and because they have other relevant functions, such as ROS elimination [95], stimulation of collagen synthesis, and inhibition of MMPs, important for maintaining youthful skin.

To determine the ability of the coprisin peptide, an AMP derived from insects, to inhibit MMP-1 expression in human fibroblasts, Kim et al. [96] developed a study, where the results demonstrated that coprisin peptide, at a concentration of 25 μM, almost completely inhibited MMP-1 expression, which makes it a potential cosmetic ingredient for anti-aging products.

Additionally, defensins for skin anti-aging are patented [97] and owned by the company DefenAge. The α-defensin-5 and β-defensin-3, in particular, are cosmetic ingredients widely used in their anti-aging products.

Thus, AMPs have great potential in the cosmetic industry, since they have an important role against skin aging, and showed low toxicity in topical application [98]. However, their mechanisms of action are not fully understood and their production cost is high. For this reason, more studies should be conducted in the future to understand their mechanism of action and to amplify their application as anti-aging cosmetic ingredients.

3.4. Other peptides

The karphyrins are fractions of peptide extracts resulting from the hydrolysis of white sorghum grain [100]. These peptides, have shown efficacy against skin aging, owing to their capacity to reduce the expression of elastase and collagenase.

In order to assess the efficacy of karphyrins in reducing elastase and collagenase activity, a study was conducted in which organotypic cultures of human skin were subjected to UVB radiation and then subjected to the action of the peptides. After exposure to UVB radiation there was an increase in collagenase (36.0 %) and elastase (166.0 %) activity in the skin, but in the presence of karphyrins, it was showed a collagenase and elastase inhibition of 25.0 % and 57.0 %, respectively, which supports their anti-aging effect [100].

3.5. Combination of anti-aging peptides

In addition to the benefits described above, peptides have yet another advantage, since they can be used in combination with other cosmetic ingredients, to potentiate anti-aging effects [49], e.g., the combination of niacinamide, palmitoyl pentapeptide-4, palmitoyl dipeptide-7, carnosine and retinyl propionate.

Retinoic acid is one of the most widely used and researched cosmetic ingredients for reversing signs of photoaging [101], however possess low skin tolerance and can cause erythema [102]. Therefore, associations of cosmetic ingredients may prove advantageous over retinoic acid when it comes to skin sensitization.

Fu et al. [103] reported a study in which 196 women with moderate to moderately severe periorbital wrinkles participated. 99 women performed a skincare routine that included 3 cosmetic products: sun protection lotion and night cream, both containing the combination niacinamide/palmitoyl pentapeptide-4/palmitoyl dipeptide-7/carnosine and a specific anti-wrinkle treatment, containing niacinamide/palmitoyl pentapeptide-4/palmitoyl dipeptide-7/carnosine/retinyl propionate (retinyl ester is less irritating) and other 97 volunteers underwent a prescription regimen in which they used 0.02 % topical retinoic acid and a sunscreen with a sun protection factor of 30. After 8 weeks, the skincare routine, was found to lead to a significant reduction in wrinkles and to have better tolerability than 0.02 % retinoic acid,

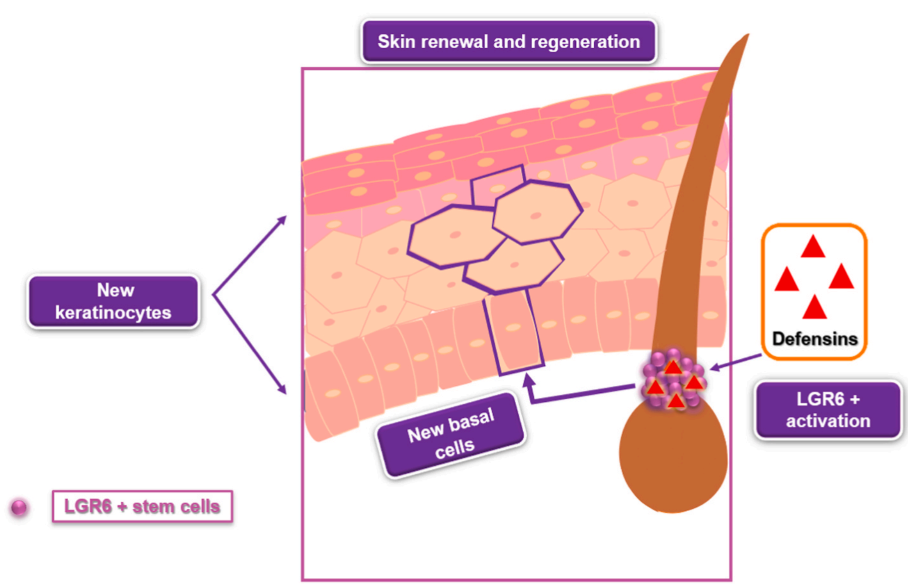

Fig. 1. Defensins activating LGR6-positive cells to stimulate the production of new keratinocytes and consequent renewal of the skin. **Adapted from:** [99].

which showed higher skin irritation and whose similar anti-aging results can only be achieved after 24 weeks. Therein, the combination niacinamide/palmitoyl pentapeptide-4/palmitoyl dipeptide-7/carnosine/retinyl propionate showed to be efficient in reducing the signs of skin aging comparable to 0.02 % retinoic acid, and with less skin irritation.

4. Technological strategies for the skin delivery of anti-aging peptides

Anti-aging peptides, as discussed earlier, have selectivity [113], still penetration through the stratum corneum is poor [10], therefore, it becomes crucial to use diversified technological strategies, to enhance their delivery to the deeper layers of the skin, ensuring their efficiency against skin aging.

4.1. Physical enhancers

Physical enhancers are strategies that aim to increase the permeability of cosmetic ingredients through the skin, i.e. allow their passage through the stratum corneum and viable epidermis and enable their subsequent delivery into the dermis [7]. This is achievable, since these methods act by modifying the barrier function of the skin, in a temporary and reversible way, consequently skin resistance is reduced, which facilitates the penetration of anti-aging peptides to their target site.

4.1.1. Microneedles

Microneedles are a promising and minimally invasive transdermal delivery technique effective in promoting peptide permeation through the skin [114]. The needles have a size ranging from 100 to 1500 μm, which makes them able to pass through the stratum corneum (thickness between 10 and 30 μm) [115]. Furthermore, they are responsible of

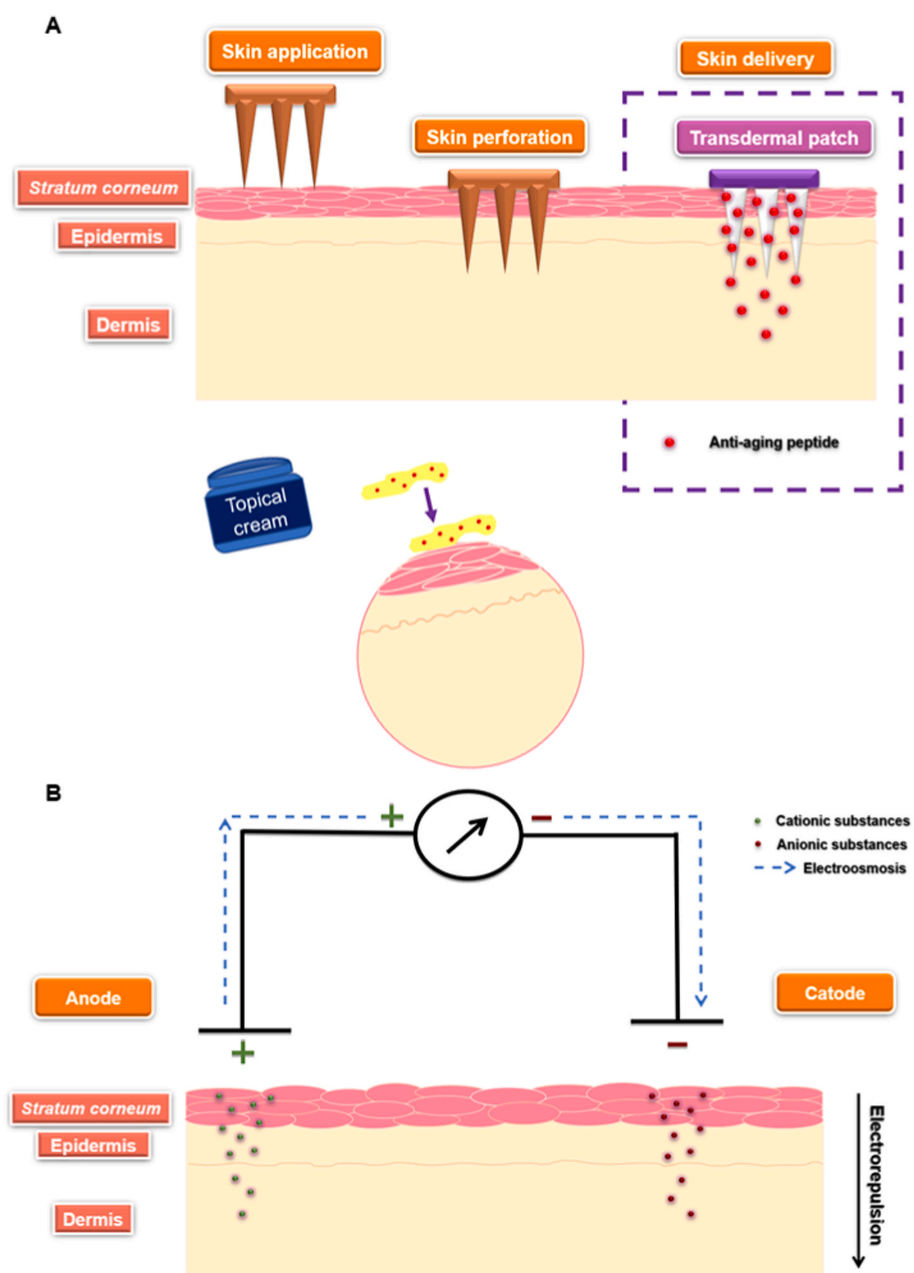

Fig. 2. Schematic representation of physical methods for the delivery of antiaging peptides. **(A)** Application with solid microneedles versus conventional topical cream. **(B)** Iontophoresis (electropulsion and electroosmosis) and movement of particles through the skin. **Adapted from:** [7].

forming pores in the skin, which are large enough to allow macromolecules to pass through, simply and painlessly [116].

Despite the advantages of this notable approach, microneedles have an obstacle when it comes to the delivery of substances: the elasticity of the skin. This parameter may hinder the penetration of microneedles in the stratum corneum, since the skin, can deform with the pressure exerted by the needle, without breaking its barrier. Consequently, pore formation and substance permeation are compromised [117].

There are some studies suggesting that different microneedles allow successful permeation of peptides into the skin [118] (see Fig. 2 (A)). An *in vitro* study was performed by Zhang et al. [119], to investigate the efficacy of solid microneedle arrays (consisting of 121 needles, attached to an applicator) in delivering hydrophilic peptides, namely acetyl hexapeptide-3, into pig ear skin. The results of the study exhibited not only that this physical system was effective in forming pores, but also in the delivery of the peptides through the skin, since the passive flow of acetyl hexapeptide 3 through the skin, when microneedles were applied was 0.44 ± 0.12 μmoL/cm/h, which was much higher than the passive flow of this peptide in untreated skin (0.014 ± 0.002 μmoL/cm/h).

4.1.2. Iontophoresis

The iontophoresis is a non-invasive technique, which consists in the application of low intensity electric current, to improve the permeability of substances through the skin [120] (see Fig. 2 (B)). This is possible, through two mechanisms: electrorepulsion, that consists of charged substances movement through the skin, under the influence of an electric field and is based on the principle that equal charges repel each other and different charges attract each other [6], i.e. positively charged substances are dissolved at the anode (electrode with the same polarity), and are repelled, so they are forced to cross the stratum corneum toward the cathode and the opposite for negative molecules [121], electroosmosis, that consists of solvent flow induced by an electric field, which consequently causes the movement of neutral or charged molecules through the skin [122]. This mechanism is particularly relevant in the permeation of higher molecular weight substances [6].

A study was performed by Krishnan et al., to assess the efficacy of iontophoresis in the permeation of several peptides, including acetyl hexapeptide-3, as well as to assess the relationship between the permeation of peptides in human skin and parameters associated with this technique, namely the permeation mechanism. For the execution of this technique, an electric current of 0.4 Ma was applied with a cathode (AgCl electrode) and an anode (silver electrode). The results of the study showed that acetyl hexapeptide-3 permeated the skin more effectively through iontophoresis, compared to other permeation technique like passive diffusion and its transdermal delivery was benefited when electroosmosis was used since this peptide is neutral and has high molecular weight [123]. Therefore, iontophoresis is a physical technique that can be successfully used for transdermal peptide delivery.

4.2. Other strategies

4.2.1. Chemical enhancers

Chemical enhancers are molecules capable of temporarily reducing the performance of the epidermal barrier, this is possible due to their interaction with the stratum corneum lipids, which is responsible for increasing the fluidity of these components [124] and consequently, favors the passage of interest molecules such as peptides through the skin.

One study conducted by Chen et al. [125] aimed to demonstrate the effect of several chemical enhancers, namely oleic acid, menthol, and camphor; in combination with microneedles, to improve the permeation of decapeptide-12. For this purpose, the following was evaluated: the penetration of decapeptide-12 through microneedles, the penetration of the peptide when subjected to modification and microneedles, and finally, the penetration of the peptide with palmitic acid and each of the chemical enhancers (5.0 % (w/v) camphor, 5.0 % (w/v) oleic acid and 5.0 % (w/v) menthol). The results of the study showed that the modification with palmitic acid in addition to 5.0 % (w/v) menthol led to the highest percentage of permeation after 24 h (about 50.0 %). Thus, we can conclude that menthol, may constitute a useful strategy for the permeation of peptides when conjugated with other techniques. However, more studies should be conducted to verify the potential of menthol, as well as other chemical enhancers (camphor and oleic acid), in the permeation of anti-aging peptides, when used alone.

4.2.2. Moieties with biological properties

Vitamin C is an important molecule for the skin since it participates in the process of collagen production. During this process, ascorbic acid acts as a cofactor of the enzymes lysyl and prolyl hydroxylase, which are responsible for the hydroxylation of lysine and proline residues, essential for stabilizing the collagen structure [53]. Thus, ascorbic acid can be conjugated with anti-aging peptides. A study by Choi et al. [126], demonstrated that the conjugate resulting from the conjugation of palmitoyl pentapeptide-4 with ascorbic acid (via a succinyl chain: see Fig. 3 (A)), was stable and less susceptible to the action of some proteases, in rat skin extracts (*in vivo* test) (Fig. 3 (C)), and when tested *in vitro* on fibroblasts the conjugate was more effective to increase collagen synthesis than ascorbic acid and palmitoyl pentapeptide-4 alone, particularly, at 100 and 1000 μM concentrations (Fig. 3 (B)). Thus, it constitutes an interesting technique to protect anti-aging peptides against early enzymatic degradation, and to stimulate collagen production.

4.3. Nanoencapsulation

With the substantial increase in demand for more effective cosmetics, it is becoming more complicated to draw a distinctive line between the skin application of a cosmetic active and a pharmaceutical active. As far as cosmetic formulations are concerned, they do not reach systemic circulation, however, for their effect to be achieved these formulations must have considerable skin penetration [127]. In this sense, the use of small functional systems at the nanoscale to incorporate their cosmetic ingredients is relevant [11]. These transport systems can overcome the limitations of conventional delivery systems [128], as they can enhance and modify the permeation of bioactive substances through the skin, allow direct contact with the stratum corneum and skin appendages, increase the contact surface of cosmetic ingredients with the corneocytes protect the substances from possible instabilities, control their release, and enlarge both dermal penetration of the active ingredient and residence time in the skin [129].

Therefore, nanodelivery systems have been the subject of great interest from the cosmetic industry [130], nonetheless, it should be noted that they offer some challenges when it comes to their use. The biggest challenge currently facing the application of nanotechnology for the transport of cosmetic ingredients is to reduce the size of the substances sufficiently to penetrate the skin, while maintaining their chemical properties, in a way that does not compromise their efficacy once delivered to the target site. Moreover, nanodelivery systems have interactions with some targets that are not fully elucidated, which could constitute a toxicological problem, but is a relevant subject of research towards optimization of the application of nanotechnology in cosmetic products [131].

4.3.1. Nanoemulsions

Nanoemulsions are dispersions with small droplet size, about 100 nm, and like other emulsions, are formed by two immiscible phases (oil phase and aqueous phase) and one or more surfactants, which ensure the stability of the dispersion [130]. These nanodelivery systems have advantages over conventional emulsions, since, given the small size of their droplets, they more easily penetrate the skin. Moreover, they are stable against sedimentation, have greater contact surface and fluidity (which allows a better spreadability), as well as, improvement in the transport and release of active ingredients, and, finally, they can be more

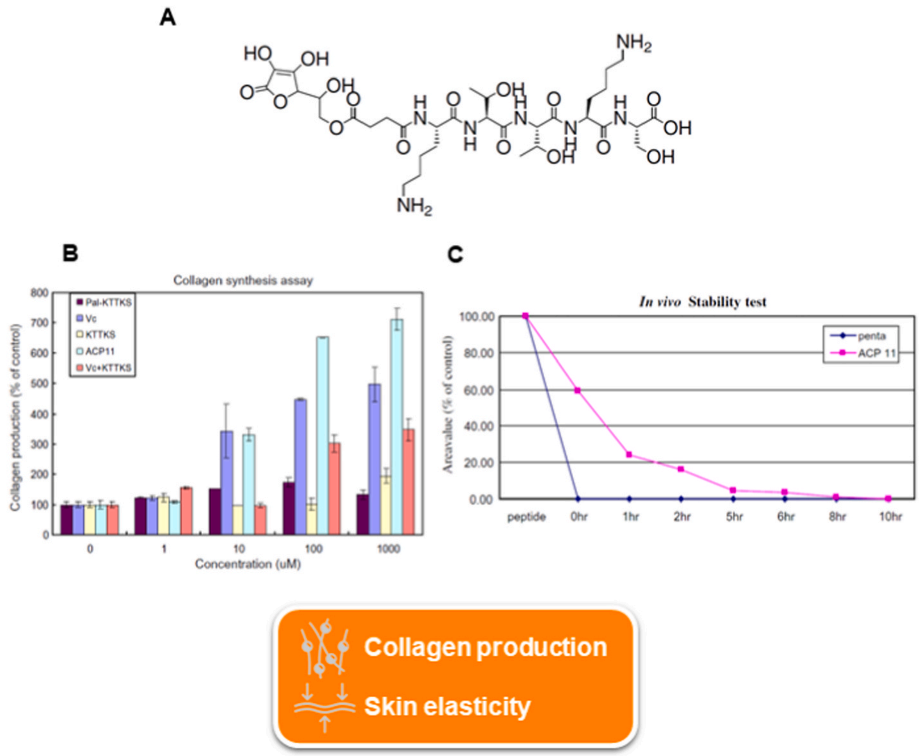

Fig. 3. Effect of ascorbyl conjugated peptide on collagen production to increase skin elasticity. **(A)** Molecular structure of ACP 11. **(B)** Production of collagen stimulated by ACP 11. Equivalent quantities of human normal fibroblast cells were exposed to several sample concentrations. Incubation occurred for 72h, and cells were retrieved and evaluated via ELISA. **(C)** *In vivo* stability test of ACP 11 in rat skin extracts. **Adapted from**: [126].
Abbreviations: ACP 11 - Ascorbyl conjugated peptide, **KTTKS** - Pentapeptide-4, **Pal-KTTKS** - Palmitoyl pentapeptide-4, **Vc** - Ascorbic acid.

appealing to apply in the skin (development of transparent formulations) [43,132]. Such aspects, justify their use in various cosmetic products, such as anti-aging preparations.

An *in vitro* study was conducted to evaluate, among other aspects, the permeation of the nanoemulsion containing Cu-GHK (0.003 % w/w). The skin was simulated by a cellulose acetate membrane and the nanoemulsion was formulated with an oil phase composed of T80:PF68 (surfactants, in a 40:1 ratio) and virgin coconut oil; and an aqueous phase containing deionized water and xanthan gum. Contour diagrams were employed in order to assess the interaction concerning the independent variables (Fig. 4 (C, D and E)). Thus, the optimized formulation contains virgin coconut oil (10.0 % w/w), T80:PF68 (15.0 % w/w), xanthan gum (0.867 % w/w) and water (74.133 % w/w); and the software predicted a particle size of 120.882 nm. Transmission electron microscope images showed that the particle size of the droplets of the optimal formulation (about 20–200 nm) have no considerable difference regarding particle size of the droplets of the formulation with copper peptide (Fig. 4 (A)). Moreover, permeation studies revealed that nanoemulsions improved the permeation of the Cu-GHK of 2.26 ± 0.09 % at 1 h, into 21.89 ± 0.53 % after 8 h of application (Fig. 4 (B)) [133].

4.3.2. Nanodelivery systems

4.3.2.1. Phospholipid-based vesicular systems. Phospholipid vesicles are one of the most versatile and valuable nanodelivery systems due to their structure and similarity to skin components. These systems can easily interact with skin layers due to their small size, elasticity, and lipid content [134].

4.3.2.2. Liposomes. Liposomes are small and spherical structures, that consist of an aqueous core surrounded by one or more phospholipid bilayers [135], made up of unsaturated or saturated phospholipids. Phosphatidylcholine, for example, is an unsaturated phospholipid, which makes the membranes more permeable and less stable when compared to using saturated phospholipids. Owing to their size, simultaneous hydrophilic and hydrophobic character, and different delivery mechanisms, namely, direct transfer from the vesicles to the skin (adsorption) or fusion with the lipid matrix of the epidermis [136], liposomes are able to transport anti-aging peptides.

Han et al. [12] conducted several studies to evaluate the potential of nanoliposomes: for simultaneous delivery of anti-aging peptides to dermal fibroblasts, as well as improving their activity. In a *in vivo* study, 45 women, aged between 25 and 55 years, were randomly divided. 15 applied a lotion containing 2.0 % of anti-aging peptides (carnosine, acetyl hexapeptide-3 and palmitoyl tripeptide-5) loaded on nanoliposomes, twice a day, for 4 weeks. Another 15 volunteers applied, in the same way, a lotion containing the free bioactive peptides, at the same dose. And finally, the remaining 15 volunteers applied a placebo lotion (no peptides and no nanoliposomes) for the same period of time. The results of the study showed that after 28 days of application, the peptides encapsulated in nanoliposomes demonstrated a higher reduction in wrinkle volume (25.0 %), area (29.4 %), and a higher increase in skin elasticity (36.6 %), when compared to the lotion containing free peptides (22.4 %, 22.4 % and 29.1 %, respectively) and placebo lotion (21.2 %, 21.8 % and 25.6 %, respectively). In an *in vitro* study was compared the release of the same peptides encapsulated in nanoliposomes, with the free peptides dispersed in a solution (see Fig. 5). The results showed that nanoliposomes allowed the release of carnosine (91.3 %), acetyl hexapeptide-3 (84.8 %) and pal-KVK (34.6 %), after 48 h. However, the release rate of peptides in nanoliposomes was slowed down compared to free peptides, which demonstrates that these transporters allow a sustained release to their site of action, providing enhanced efficacy.

4.3.2.3. Ethosomes. Ethosomes are nanovesicles that consist of an inner aqueous portion surrounded by a phospholipid bilayer [137], but are

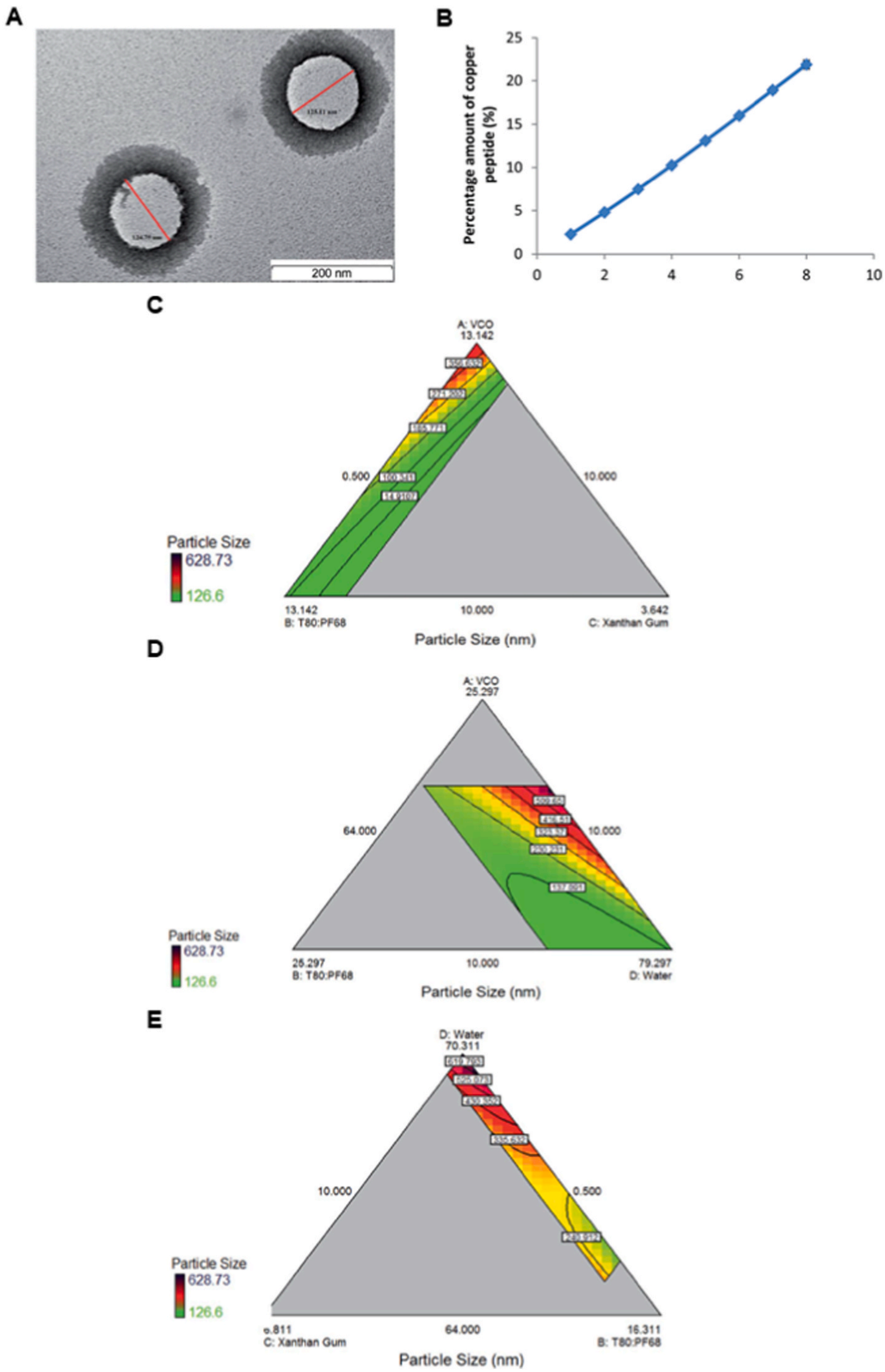

Fig. 4. (A) Transmission electron microscope images of virgin coconut oil nanoemulsion containing 0.003 % (w/w) copper peptide **(B)** *In vitro* permeation profile for VCO nanoemulsion containing copper peptide. **(C)** Contour diagram showing the interaction effect between three variables: VCO, T80:PF68, and xanthan gum; with water maintained constant. **(D)** Contour diagram showing the interaction effect between three variables: VCO, T80:PF68, and water; with xanthan gum maintained constant. **(E)** Contour diagram showing the interaction effect between three variables: water, xanthan gum, T80:PF68; with VCO maintained constant. **Adapted from**: [133].
Abbreviations: VCO - Virgin coconut oil.

distinguished from these structures by the presence of high concentrations of ethanol (20.0–45.0 % v/v) [138], which gives them unique properties, particularly with regard to penetration through the skin [136].

Ethanol is a chemical promoter of substance permeation through the skin, but can cause disruption of the *stratum corneum* [139]. This is possible through its interaction with the hydrophilic head of the matrix lipids, which generates a change in the conformation of these structures temporarily, and makes skin lipid layer more fluid, and consequently, more permeable to anti-aging peptides. After the ethanol has acted, the ethosomes are able to penetrate through the stratum corneum, whose barrier function is reversibly compromised, and fuse into the deeper layers of the skin, releasing the active ingredient [140].

A study was designed by Kim et al. [141], to evaluate the transdermal

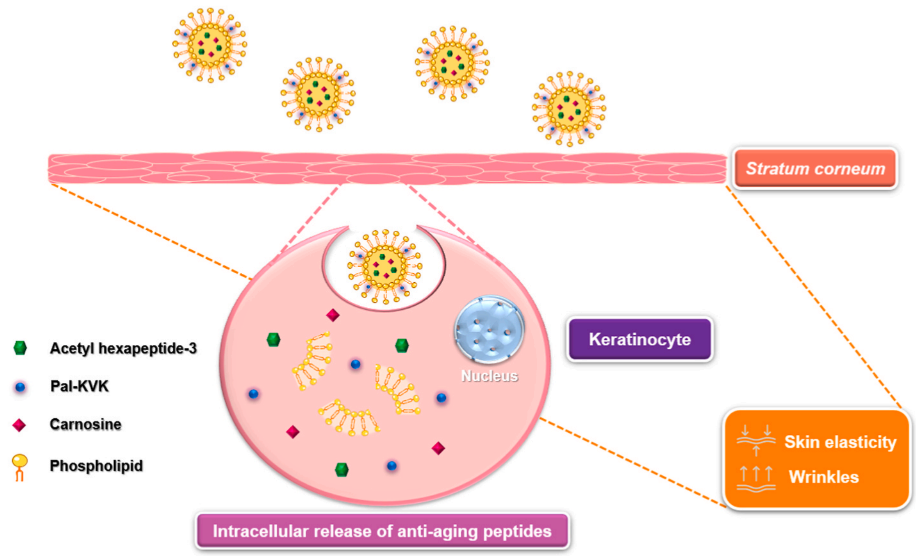

Fig. 5. Schematic representation of the study: nanoliposomes penetration through skin, co-delivery of anti-aging peptides (carnosine, acetyl hexapeptide-3 and pal-KVK) and release of the same peptides. **Adapted from:** [12]
Abbreviations: **Pal-KVK** - Palmitoyl tripeptide-5.

delivery of palmitoyl pentapeptide-4 via a novel ethosome, called transformer-ethosome. The transformer-ethosome had in its composition, ethanol, soy phosphatidylcholine and fatty acids. The results obtained, through an imaging technique with fluorescence marker (rhodamine-6G), demonstrated that a 15.0 % ethanolic solution allowed peptide penetration into the stratum corneum, conventional liposomes and ethosomes allowed peptide penetration into the basal layer of the epidermis and finally, the transformer-ethosome allowed penetration of the palmitoyl pentapeptide-4 into the dermis, due to the presence of myristic acid and capric acid in the phospholipid bilayer, which may confer greater fluidity to the structure and hence permeability of the palmitoyl pentapeptide-4 through the skin.

Hence, ethosomes have proven to be a noteworthy nanodelivery system, but there is a considerable disadvantage that must be considered during the formulation of cosmetic products, which is the volatility of ethanol, that put at risk the system stability. Also, ethanol is an organic solvent with high skin irritation potential.

4.3.2.4. Niosomes. Niosomes are vesicular systems, with spherical shape and structure similar to liposomes, and they differ from them, mainly owing to their composition (made of non-ionic surfactants and cholesterol) [142]. The use of non-ionic surfactants proves to be an advantage for these systems, given the diverse functions of these components, as well as their constitution, since they can perform several functions, as solubilizers, humectants or permeability enhancers [143]. Additionally, niosomes contain cholesterol, a component that affects the fluidity and permeability of the bilayer and protects the active ingredients [144].

A pre-formulation study was conducted by Badenhorst et al. [145] to evaluate some physicochemical characteristics of the Cu-GHK peptide to be applied in a novel anti-aging product. Throughout the study, to verify the compatibility of Cu-GHK with niosomes, the stability of Cu-GHK was analyzed after exposure to constituents that integrate the structure of niosomes, particularly cholesterol and Span 60, at 40 °C for a period of 4 weeks (which occurred during preparation and storage). The results of the study displayed that in the presence of these excipients, for 4 weeks, CU-GHK did not suffer degradation. Although niosomes may constitute viable nanodelivery systems for dermal delivery of anti-aging peptides further studies should be conducted, in order to assess their performance and efficacy.

4.3.3. Polymeric nanodelivery systems

Polymeric nanoparticles or polymeric nanodelivery systems, are nanoparticles that have in their composition natural polymers such as chitosan or synthetic polymers like (poly) lactic acid. Depending on their composition, these be called nanocapsules when formed by an aqueous or oily core, which contains the active ingredient, surrounded by a polymeric shell, or nanospheres, when the active ingredient is dispersed uniformly in a polymeric matrix [146].

Nanoparticles have features that justify the growing demand for these nanodelivery systems, e.g., the use of polymers that allow encapsulation of cosmetic ingredients, the masking of unfavorable physicochemical properties of these substances, as well as improve their penetration through the skin [131].

However, they have some unfavorable aspects, particularly safety concerns, since there are few studies about their effects when used in cosmetics and applied in long-term in periods [146]. Still, polymeric nanoparticles are applied in the cosmetic industry, for topical delivery of cosmetic ingredients, with greater precision and efficiency, namely anti-aging peptides [147].

The Eye Tender serum by Kara Vita, is an anti-aging product [129] and an example of the application of polymeric nanoparticles, namely nanospheres for the delivery of anti-aging peptides, that can be responsible for stimulating fibroblasts to produce collagen [147].

5. Concluding remarks

The anti-aging peptides, as discussed throughout this review, are currently available in the formulation of various cosmetics, including Nº7 Protect & Perfect Intense Beauty Serum™ (that include palmitoyl oligopeptide and palmitoyl tetrapeptide-7) [148], Dermican™ (which has acetyl tetrapeptide-9), Syniorage™ (with acetyl tetrapeptide-11) and Serilesine® (with hexapeptide-10) [104], among others.

Nevertheless, despite their high potential and great media focus, there are not many studies available in the literature about anti-aging peptides, in particular regarding the mechanism of action of enzyme-inhibiting peptides, neurotransmitter inhibitor peptides and antimicrobial peptides, as well as the ability of peptides to permeate through the skin when encapsulated in nanodelivery systems. Nanodelivery systems, due to their stability, biocompatibility, and efficiency in dermal delivery, are used for the transport of these peptides, yet further studies should be carried out to assess, not only the efficacy of peptides when transported by these nanocarriers, but also their penetration through the skin.

Hence, these peptides show to be interesting molecules against skin aging and although they do not replace the use of sunscreens (primary prevention care against the action of UV radiation) or retinoids (standard anti-aging active ingredients), which are first-line products against skin aging; these cosmetic ingredients boost and complement their action, and they are a consistent and exceptional alternative for sensitive and retinoids-intolerant skin.

6. Futures perspectives

Owing to their multiple mechanisms of action, safety and valuable effects for the skin, peptides are increasingly sought after to prevent skin aging, and are outstanding cosmetic ingredients for the development of new and/or for the enhancement of conventional cosmetic formulations, possessing several applications. When it comes to rinse-off products, peptides show low efficacy given the short time of contact with the skin. However, when used in leave-on products as serums, creams or masks, anti-aging peptides act as a moisturizers, as they possess good humectant capacity, improved skin hydration and can help in the repair, softness and reinforce of the epidermal barrier.

The use of peptides in the cosmetic care of skin aging offers, as demonstrated by the various studies presented throughout this article, several advantages including: prevention of premature aging, reduction of damage caused by ultraviolet radiation, stimulation of matrix protein production, reduction of pigmentation, decrease in roughness and improvement of elasticity and firmness. Nowadays, new peptide formulations emerge promising to fight the most common signs of aging, being "Lightskin" an example. This product is commercially available and seems to effectively reduce melanogenesis, once it possesses sulfur containing-peptides produced by *Ogataea siamensis* yeast, through biotechnological process. However, the information available so far does not allow to draw further conclusions about the efficacy of these peptides [149].

Therefore, further research in the field of anti-aging peptides is expected to expand their use in cosmetics and understand the magnitude of their applications and mechanisms of action. Likewise, new methods of transport through the skin, mainly nanodelivery systems will be developed, since they have already been shown to be effective in the skin delivery of peptides, though they have not yet been studied more in depth for anti-aging peptide applications.

Overall, anti-aging peptides and nanodelivery systems have displayed promising results against the signs of aging, since these carriers can penetrate the skin at a deeper level and modified the release of the active ingredient, allowing for better absorption and longer-lasting effects, i.e. reducing visible signs of skin aging such as wrinkles, fine lines, and hyperpigmentation. Nevertheless, more research is needed to fully understand their long-term effects and safety, with the aim of delay skin aging and promote better health and quality of life.

In the following years, mainly two trends are expected: products designed to balance the microbiome and to get a healthier skin, with proper healing and functional epidermal barrier, so AMPs may be playing a big role in this cosmetic segment. Another trend is the concept of skin minimalism, in which anti-aging peptides will be particularly prominent, due to their multifunctionality, applications and vast combinations among themselves and with other cosmetic ingredients (antioxidants, vitamins and their derivatives, humectants), ensuring a broad spectrum of action, improving the efficacy and safety of the products, and reducing the number of products necessary for skincare routine. Additionally, clinical applications of anti-aging peptides and nanodelivery systems for skincare will firmly cover the development of targeted therapies for skin disorders, improved wound healing strategies and non-invasive skin rejuvenation methods.

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CRediT authorship contribution statement

Eliana Veiga: Conceptualization, Writing – original draft, Software. **Laura Ferreira:** Conceptualization, Writing – original draft, Software. **Mafalda Correia:** Writing – original draft. **Patrícia C. Pires:** Writing – original draft. **Huma Hameed:** Writing – review & editing. **André R.T. S. Araújo:** Writing – review & editing. **Letícia Caramori Cefali:** Supervision, Writing – review & editing. **Priscila Gava Mazzola:** Supervision, Writing – review & editing. **Hamed Hamishehkar:** Supervision, Writing – review & editing. **Francisco Veiga:** Funding acquisition, Conceptualization, Supervision, Writing – review & editing. **Ana Cláudia Paiva-Santos:** Funding acquisition, Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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