Article

Trending Anti-Aging Peptides

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Abstract: The development of synthetic peptides for skin care dates to the 1980s. The cosmetic industry periodically launches new peptides, as they are promising and appealing active ingredients in the growing and innovative cosmetics market. In this study, trends in the use of peptides in anti-aging products were analyzed by comparing the composition of the products marketed in 2011 with products launched or reformulated in 2018. The scientific and marketing evidence for their application as active ingredients in anti-aging cosmetics was also compiled from products' labels, suppliers' technical data forms and online scientific databases. The use of peptides in anti-aging cosmetics increased by 7.2%, while the variety and the number of peptide combinations in products have increased by 88.5%. The most used peptides in antiaging cosmetic formulations are, in descending order, Palmitoyl Tetrapeptide-7, Palmitoyl Oligopeptide and Acetyl Hexapeptide-8. In 2011, the majority of peptides were obtained from synthesis, while in 2018, biotechnology processing was the dominant source. This study provides an overview of the market trends regarding the use of peptides in anti-aging products, providing meaningful data for scientists involved in the development of new peptides to identify opportunities for innovation in this area.

Keywords: peptides; anti-aging; cosmetics; skin care; biotechnology; trends

1. Introduction

The anti-aging market is expected to grow at an approximate 8% compound annual growth rate between 2018 and 2021, reaching a value of USD 271.0 billion by 2024 [1]. As the competition increases among cosmetic brands from the anti-aging market, new products claim to contain the ultimate innovations in order to stand out, often advertising new active ingredients.

Glutathione was the first biological peptide synthesized in the laboratory, and the development of new synthetic methods allowed for the synthesis of longer peptide chains, such as oxytocin and insulin [2]. Although peptides are distinguished from proteins by their shorter length, the cut-off number of amino acids to establish the classification as peptide is arbitrary [3]. According to the Food and Drug Administration (FDA), which is responsible for the regulation of health products, proteins are amino acid polymers with a specific defined sequence that is greater than 40 amino acids in size [4]. Peptides became popular in cosmetic products due to their bioactive properties, as they are able to interact with skin cells by multiple mechanisms, present high potency at low dosage and because their size is thought to achieve a moderate penetration into the upper skin layers. Due to their hydrophilic properties, chemical modifications such as esterification with alkyl chains, may be required to enhance penetration [5,6]. Furthermore, there are peptides whose structure is inspired by naturally occurring

molecules, such as matrikines originating from the fragmentation of extracellular matrix, which is a relevant trend in the cosmetic industry [7]. However, most peptides are actually obtained by chemical synthesis or biotechnology processing [8].

Peptides started being incorporated in cosmetic products during the late 1980s with the use of copper glycine-histidine-lysine (Cu-GHK). However, these ingredients did not earn notoriety in cosmetic products until the beginning of 2000, when Palmitoyl Pentapeptide-4 was launched, proposing to reduce facial wrinkles [9].

Currently, there are a wide variety of peptides available as cosmetic ingredients, which can be categorized according to their mechanism of action [6,8–11]:

- Signal peptides, which stimulate matrix protein production (such as collagen and elastin) and cell growth, amongst other cell metabolic functions (e.g., Palmitoyl Tetrapeptide-7, Palmitoyl Pentapeptide-4);
- Carrier peptides, which may act as transportation facilitators for important substances or trace elements inside the cell, such as copper and magnesium (e.g., Tripeptide-1, GHK-Cu);
- Neurotransmitter-inhibiting peptides, which may target expression wrinkles by inhibiting acetylcholine release at the neuromuscular junction by acting on distinct molecular targets (e.g., Acetyl Hexapeptide-8, Acetyl Octapeptide-3);
- Enzyme-inhibiting peptides, which may reduce the activity of enzymes that participate in skin aging (e.g., soybean peptides which inhibit serine proteases, such as matrix metalloproteinases, (MMPs), and silk peptides, which inhibit tyrosinase).

Regarding safety, although some proteins are linked to skin allergy, including contact dermatitis, we were unable to find any evidence that peptides used in cosmetics may raise any concerns in this regard [12,13]. Moreover, protein hydrolysates, which contain bioactive peptides, are categorized as Generally Recognized as Safe (GRAS) by the FDA [7].

Nowadays, the "European glossary of common ingredient names for use in the labelling of cosmetic products" contains 848 entries with the word "peptide" [14]. Given the vast diversity of peptides available for cosmetic products, this study aimed to understand how the composition of anti-aging formulations has changed in recent years for these ingredients. For this purpose, an exploratory analysis of a pool of anti-aging products corresponding exclusively to multinational brands was performed. To our knowledge, this is the first study to describe the trends in the composition of cosmetic products on the market regarding anti-aging peptides.

2. Materials and Methods

2.1. Data Collection

Data were collected from anti-aging products from multinational manufacturers, marketed in parapharmacies and pharmacies from Portugal. Anti-aging cosmetics were included in the study if they exhibited on the label one of the following words: anti-wrinkle(s); anti-age/anti-aging; wrinkle repair; regenerator; aging; anti-slackening; firming. All the information available on the products' labels was collected from the manufacturers' websites. The data collection started in 2011 and was updated with products launched in 2018 or whose composition has been reformulated that year in order to avoid duplicate product analysis and to reflect the market trends. Cosmetics for application on the face, neck and eye contour were included, comprising more than 40 multinational brands. Following these criteria, 280 products were selected, 177 and 103 in 2011 and 2018, respectively.

2.2. Data Analysis

The peptides contained in the cosmetic products collected during the study were listed according to the International Nomenclature of Cosmetic Ingredients (INCI) and commercial names. Afterwards, the data were analyzed with respect to the following parameters.

2.3. Peptides' Prevalence and Combinations

The relative amount of cosmetic products containing peptides and the occurrence of combinations of these ingredients were assessed and expressed in percentage.

2.4. Top Peptides

The analysis focused on the twelve peptides with the highest usage frequency among the selected products in both years. The overall usage frequency for each peptide was determined by the sum of the number of products containing that specific ingredient in 2011 and 2018, and then they were ranked in descending order.

2.5. Peptides' Sources

Peptides were categorized according to their sources, based on the information provided by the manufacturer or mentioned in scientific literature.

2.6. Peptides' Mechanisms of Action and Scientific Evidence

All peptides found in the periods of analysis were categorized according to the mechanism of action [9,15]. The anti-aging benefits of each peptide were searched on the following online databases: PubMed, Google Scholar, Scopus, Cochrane and KOSMET, using the following keywords: "peptide INCI name" AND ("skin" OR "topical") AND aging. Given the innovative nature of these ingredients and the lack of peer-reviewed articles for some of the peptides found in marketed products, the manufacturers' technical data sheets and brochures were also analyzed.

## 3. Results

3.1. Peptides' Prevalence and Combinations

Between 2011 and 2018, the percentage of anti-aging cosmetic products containing peptides was raised from 23.5% to 25.2% (Figure 1). Furthermore, the number of products containing two or more peptides was also raised from 8.2% to 15.5%, showing an 88.5% increase.
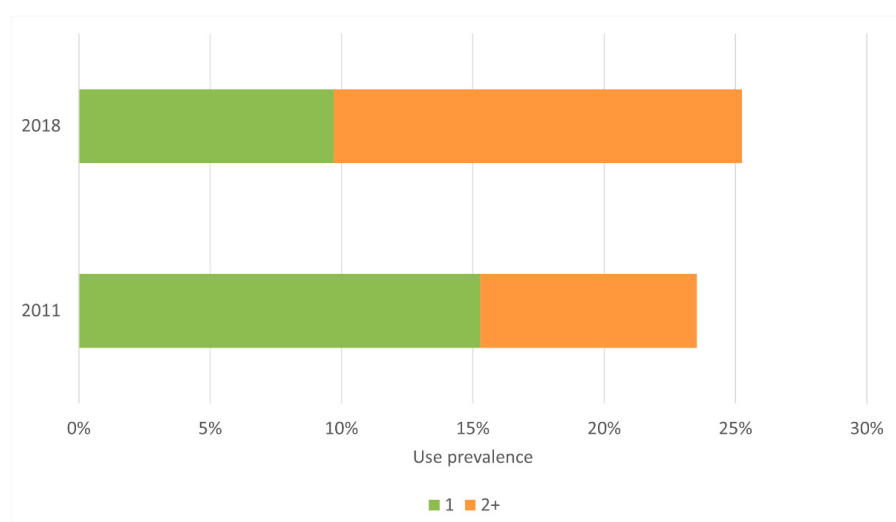
Figure 1. The prevalence of products containing peptides on anti-aging products marketed in 2011 and 2018. The percentage of products containing only one peptide (1) is represented in green, and the percentage of products containing two or more peptides (2+) is represented in orange. In 2018, there was also a greater diversity of peptides amongst anti-aging cosmetic products, as we were able to identify 29 different peptides versus the 14 peptides identified in 2011 (not illustrated), which represents more than a two-fold increase. Overall, 37 different peptides were used.

3.2. Top Peptides

Overall, the most used peptides during the seven-year period for anti-aging cosmetics were Palmitoyl Tetrapeptide-7, Palmitoyl Oligopeptide, Nicotiana benthamiana Hexapeptide-40 SH-Oligopeptide-1 and Palmitoyl Tripeptide-1 (Figure 2).
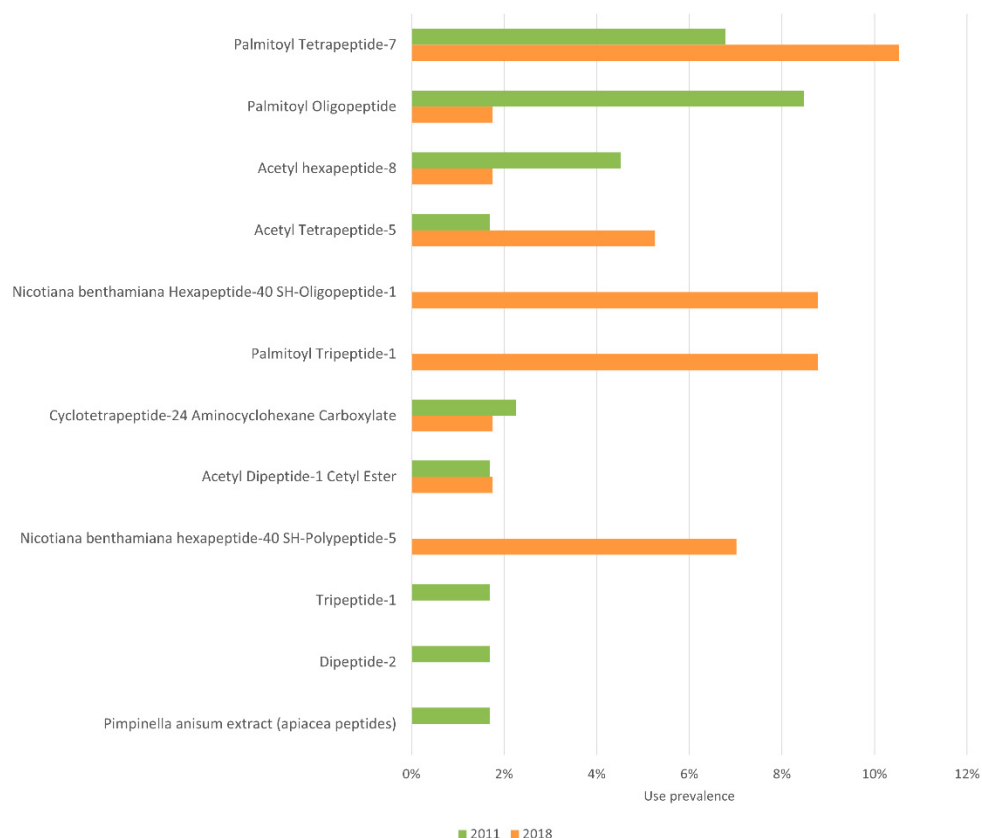
Figure 2. Top peptides included in the composition of anti-aging products marketed in 2011 and 2018.

In 2011, the most used peptides were Palmitoyl Oligopeptide, Palmitoyl Tetrapeptide-7 and Acetyl Hexapeptide-8. In 2018, the pole positions were occupied by Palmitoyl Tetrapeptide-7, *Nicotiana benthamiana* Hexapeptide-40 SH-Oligopeptide-1 and Palmitoyl Tripeptide-1.

Tripeptide-1, Dipeptide-2 and *Pimpinella anisium* extract (apiacea peptides) were used in 2011 but did not appear in products launched in 2018.

3.3. Peptides Sources

The majority of peptides launched in 2011 are obtained through chemical synthesis (Figure 3). Conversely, in 2018, there were more peptides that originated from biotechnology than synthetic ones. It is noteworthy that there is a significant amount of peptides found in both years whose source is unknown.

3.4. Peptides' Mechanisms of Action and Scientific Evidence

Signal peptides were the most used in both years, followed by neurotransmitter-inhibiting and carrier peptides (Figure 4). Contrary to the signal and carrier categories, the use of neurotransmitter-inhibiting peptides seems to be decreasing. We were unable to find enzyme-inhibiting peptides in this analysis.
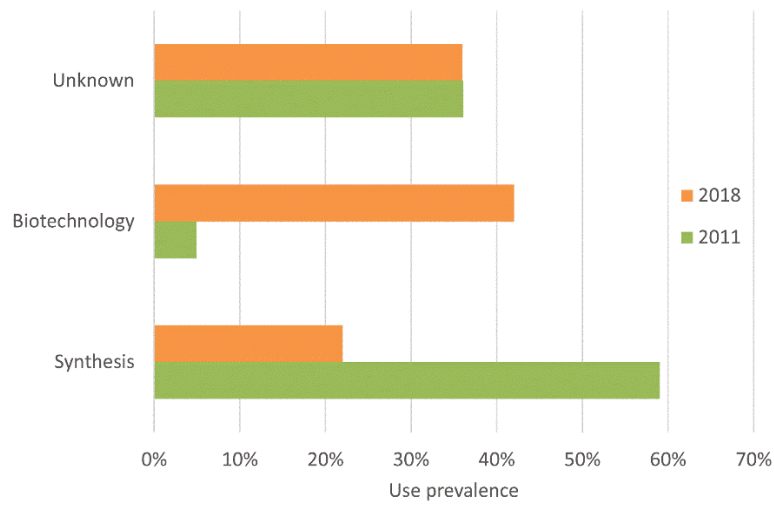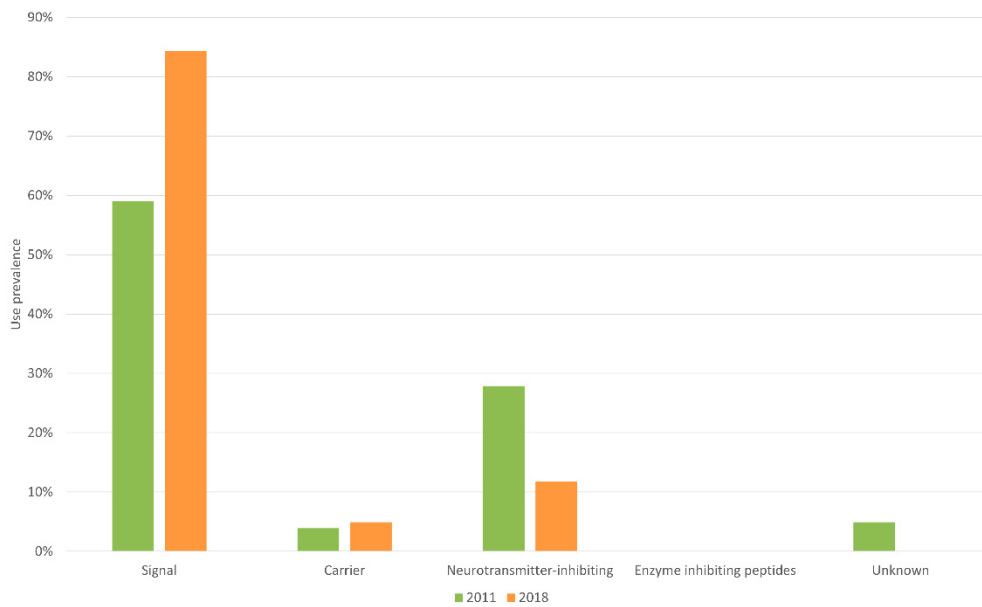
Figure 3. Sources of peptides.

Figure 4. Mechanisms of action for peptides found in anti-aging products marketed in 2011 and 2018.

The information regarding all peptides present in the composition of the analyzed anti-aging products is summarized on Table 1.

Table 1. Summary of bioactive peptides used in anti-aging products marketed in 2011 and 2018.

Category	Peptide (INCI)	Commercial Name	Source	Biomolecular Inspiration	Molecular Target	Mechanism of Action	Effect	Type of Study	Reference
Signal	Palmitoyl Oligopeptide	Matrixyl 3000 ® with Palmitoyl Tetrapeptide-7 (Sederma), Biopeptide-CL™, Biopeptide-EL™ *	Synthesis	Palmitoyl Tripeptide-1: fragment of type I collagen Palmitoyl Hexapeptide-12: fragment of elastin	Acting on TGF to stimulate fibrillogenesis	Stimulation of collagen synthesis and decrease in elastin synthesis.	Anti-wrinkle.	In vitro study **	[8,15,16]
	Palmitoyl Tetrapeptide-7	Eyeliss™ with Dipeptide-2 (Sederma), Matrixyl 3000™ with Palmitoyl Tripeptide-1 (Sederma)	Synthesis	Fragment of immunoglobulin G	Unknown	Reduction in IL-6 secretion by keratinocytes, with subsequent inhibition of the inflammatory process resulting in the degradation of the extracellular matrix.	Skin elasticity, firmness and softness increase.	Randomized-vcontrolled study **	[15,17]
	Cyclotetrapeptide-24 Aminocyclohexane Carboxylate	RonaCare® Cyclopeptide-5 (Merck KGaA)	Unknown	Ligand of the integrin in the RGD site	Unknown	Inhibition from the activity of MMPs, such as collagenase and elastase. Stimulation from the stability of the extracellular matrix by the activation of fibrilin, laminin and collagen.	Skin elasticity and firmness improvement. Wrinkle reduction.	Randomized-controlled study **	[18]
	Peptide PP	Collagen Peptide-PP (CNA Biotech)	Biotechnology	Hydrolyzed extensin from oyster mushroom, *Pleurotus ostreatus*	Unknown	Unknown	Unknown	Unknown	[19]
	Peptide PCP	Collagen Peptide-PCP (CNA Biotech)	Biotechnology	Peptide PP + peptide CP, hydrolyzed extensin from carrot, *Daucus carota*	Unknown	Unknown	Unknown	Unknown	[19]
	Tripeptide-10 Citrulline	Decorinyl® (Lipotec), Trylagen® with Tripeptide-1 (Lipotec)	Biotechnology	Similar to the decorin portion binding to collagen fibrils	Collagen fibers	Regulation from collagen fibrillogenesis and remodeling in fiber organization by binding to the collagen protein core.	Skin softness and firmness increase.	Ex vivo study **	[8]

Table 1. *Cont.*

Category	Peptide (INCI)	Commercial Name	Source	Biomolecular Inspiration	Molecular Target	Mechanism of Action	Effect	Type of Study	Reference
	Palmitoyl Tripeptide-1	Haloxyl™ with Palmitoyl Tetrapeptide-7 (Sederms), Matrixyl 3000™ with Palmitoyl Tetrapeptide-7 (Sederma)	Unknown	Fragment of type I collagen	Suggested to act on TGF.	Synthesis in collagen and glycosaminoglycans via signaling. Activity similar to retinoic acid.	Skin texture improvement and wrinkle reduction, particularly on the forehead and the crow's feet.	Randomized, controlled study **	[9,15,20]
	Palmitoyl Tripeptide-38	Matrixyl synthe'6™ (Sederma), Volulip™ (Sederma)	Unknown	KMK tripeptide derivative found naturally in collagen VI and laminins	Unknown	Stimulation of the synthesis of extracellular matrix compounds, namely hyaluronic acid, collagen I, III and IV, laminins and fibronectin.	Wrinkle reduction, particularly on the forehead and the crow's feet.	Randomized, controlled study **	[21]
	Palmitoyl Pentapeptide-4	Pal-KTTKS (u Reb Technology), SpecPed® PP4P (Spec-Chem Industry Inc.)	Synthesis	Similar to type I collagen precursor	Unknown	Stimulation from elastin, fibronectin, glycosaminoglycans as well as types I, III and IV collagen synthesis.	Skin roughness and fine wrinkle reduction.	Randomized double-blind controlled study	[8,9,22]
	Acetyl Tetrapeptide-11	Syniorage™ (BASF)	Synthesis	Unknown	Unknown	Stimulation of syndecan-1 synthesis, involved in the cohesion between cells and type XVII collagen; as well as keratinocyte growth.	Skin firmness and thickness increase.	Randomized, controlled study **	[8,9,23]
	Acetyl Tetrapeptide-9	Dermican™ (BASF)	Synthesis	Unknown	Unknown	Stimulation of type I collagen and lumican synthesis, thus improving fiber organization.	Skin firmness and thickness increase.	Randomized, controlled study **	[8,9]
	Pentapeptide-34	Peptide Q10™ Biofunctional (Ashland)	Biotechnology	Unknown	Unknown	Stimulation of coenzyme Q10 synthesis, with antioxidant action.	Cell membrane and protein preservation for skin wrinkle and roughness reduction.	Randomized, controlled study **	[24]
	Nicotiana benthamiana Hexapeptide-40 SH-Oligopeptide-1	plant-EGF, Epitensive™ (Lipotrue)	Biotechnology	EGF	Unknown	Stimulation of collagen, elastin and fibronectin synthesis; as well as keratinocytes and fibroblasts proliferation.	Anti-wrinkle and anti-sagging.	Randomized, controlled study **	[25]

Table 1. *Cont.*

Category	Peptide (INCI)	Commercial Name	Source	Biomolecular Inspiration	Molecular Target	Mechanism of Action	Effect	Type of Study	Reference
	Nicotiana benthamiana Hexapeptide-40 SH-Polypeptide-5	Unknown	Biotechnology	TGF-β3	Unknown	Unknown	Unknown	Unknown	Product label
	Nicotiana benthamiana Hexapeptide-40 SH-Polypeptide-76	plant-TGF β2, Reneseed™ (Lipotrue)	Biotechnology	TGF-β2 (granulocyte-macrophage colony-stimulating factor (GM-CSF)) from biotechnology	Unknown	Stimulation of type I collagen and fibronectin synthesis; as well as fibroblast proliferation.	Wrinkle reduction.	Randomized, controlled study **	[25,26]
	Nicotiana benthamiana SH-Polypeptide-45	MULTIEFFECT 3R (Plantaderma)	Biotechnology	GM-CSF	Unknown	Stimulation of type I collagen and total protein synthesis as well as the proliferation of keratinocytes and fibroblasts.	Skin repair and rejuvenation.	Unknown	[27]
	Nicotiana benthamiana Hexapeptide-40 SH-Polypeptide-9	NEX-VEGF121 (NEXGEN Biotechnologies, Inc.)	Biotechnology	VEGF	Unknown	Hair growth stimulation by promoting nutrient delivery to the hair follicle. Angiogenesis induction.	Unknown	Unknown	[28]
	Nicotiana benthamiana SH-Polypeptide-7	MULTIEFFECT R+D (Plantaderma)	Biotechnology	HGH	Unknown	Reduction in fibroblast proliferation and melanin synthesis.	Skin whitening, rejuvenation, repair and thickening.	Unknown	[29]
	Nicotiana benthamiana SH-Oligopeptide-2	Anargy™ with Nicotiana Benthamiana Hexapeptide-40 sh-Polypeptide-9 and Nicotiana Benthamiana Hexapeptide-40 sh-Polypeptide-86 (Lipotrue)	Biotechnology	IGF-1	Unknown	Unknown	Unknown	Unknown	-
	Nicotiana benthamiana Hexapeptide-*40* SH-Polypeptide 2	Pureoxin (Lipotrue)	Biotechnology	TRX	Unknown	Antioxidant.	Complexion improvement and wrinkle reduction.	In vitro study **	[30]
	Nicotiana benthamiana SH-Polypeptide-15	Unknown	Biotechnology	TIMP-2	Unknown	Unknown	Unknown	Unknown	Product label

Table 1. *Cont.*

Category	Peptide (INCI)	Commercial Name	Source	Biomolecular Inspiration	Molecular Target	Mechanism of Action	Effect	Type of Study	Reference
	Tripeptide-32	Chronolux™ (Ashland)	Unknown	Unknown	Gene PER1 or CLOCK	Circadian rhythm regulation and stimulation of synthesis of cell repair proteins.	Wrinkles and fine lines reduction.	Unknown	[31]
	Trifluoroacetyl Tripeptide-2	Progeline™ (Lucas Meyer Cosmetics)	Synthesis	Unknown	Elastase MMP	Reduction in elastase MMP and progerin synthesis. Proteoglycan synthesis stimulation and collagen contraction.	Skin roughness and wrinkles reduction, particularly on the forehead and crow's feet.	Ex vivo study **	[8,9]
	Hexapeptide-10	Serilesine® (Lipotec)	Synthesis	Alpha chain sequence of laminin-I	Unknown	Increase in cell proliferation and V-laminin synthesis stimulation.	Dermis redensification for skin elasticity and firmness improvement.	Randomized, controlled study **	[15,32]
Neurotransmitter-inhibiting	Acetyl Hexapeptide-8 or Acetyl hexapeptide-3	Argireline® (Lipotec)	Synthesis	Mimics SNAP-25 N-terminal	Soluble NSF attachment receptor (SNARE) complex	Reduction in acetylcholine release by inhibition of the SNARE complex.	Inhibition of muscle contraction for and anti-wrinkle action.	Randomized, controlled study	[8,33]
	Acetyl Dipeptide-1 Cetyl Ester	Calmosensine™ (Sederma)	Synthesis	Unknown	Unknown	Stimulation of met-enkephalin release, opioid by promotion of the expression from the gene Expression Pro-opiomelanocortin.	Reduction in skin irritation due to heat, stinging upon contact with chemical irritants and mechanical stress. Wrinkle and expression line prevention due to its muscle relaxation properties.	Randomized, controlled study	[28]
	Acetyl Tetrapeptide-5	EYESERYL®, SpecKare™ Eye S100 with Dipeptide-2 (Lipotec)	Unknown	Unknown	ACE	ACE inhibition.	Eye contour oedema reduction	Randomized, controlled study **	[15,34]

Table 1. *Cont.*

Category	Peptide (INCI)	Commercial Name	Source	Biomolecular Inspiration	Molecular Target	Mechanism of Action	Effect	Type of Study	Reference
	Dipeptide-2	SpecKare™ Eye S100 with Acetyl Tetrapeptide-5 (Spec-Chem Industry Inc.), Eyeliss™ with Palmitoyl Tetrapeptide-7 (Sederma)	Synthesis	Unknown	ACE	ACE inhibition.	Lymphatic drainage of the eye contour and telangiectasias reduction.	Randomized, controlled study **	[15,34]
	Acetyl Octapeptide-3	SNAP-8™ (Lipotec)	Synthesis	Elongation of acetyl hexapeptide-8	Soluble NSF attachment receptor (SNARE) complex	Reduction in acetylcholine release by inhibition of the SNARE complex.	Inhibition of muscle contraction for and anti-wrinkle action	Randomized, controlled study **	[15,35]
Carrier	Tripeptide-1	Aldenine® (Lipotec), Trylagen® with Tripeptide-10 Citrulline (Lipotec)	Synthesis	Present on blood	Copper	Copper transport for collagen, elastin, proteoglycans and glycosaminoglycans synthesis increase.	Antioxidant action, dermis redensification and skin repair.	Unknown	[8]
	Diaminopropionoyl Tripeptide-33	PREVENTHELIA® (Lipotec)	Synthesis	Obtained from a peptide library	4-hydroxynenal	Chelation from of 4-hydroxynenal resulting from lipid peroxidation.	Prevention from cell damage due to ROS.	In vitro study **	[36]
	Tripeptide-9 Citrulline	dGLYAGE® (Lipotec)	Synthesis	Unknown	Copper	Chelation from copper and prevention of ROS formation.	Prevention from cell damage due to ROS.	In vitro study **	[37]
Unknown	*Nicotiana benthamiana* sh-polypeptide-15 hexapeptide-40	Unknown	Biotechnology	Unknown	Unknown	Unknown	Unknown	Unknown	-
	Pimpinella anisum extract (apiacea peptides)	Unknown	Unknown	Unknown	Unknown	Increase in the levels of enzymes which are essential to break down and remove damaged cells.	Promotion of skin renewal and strengthening from connective tissue. Improvement microcirculation and skin density radiance.	Unknown	[38]
	Pentapeptide-28	Chondricare™ IS biofunctional (Ashland)	Synthesis	Unknown	Aconitase	Increase in the enzymatic activity of aconitase and stimulates cell vitality	Increase in cell energy production.	Unknown	[39]

* After the renaming of Palmitoyl Oligopeptide, it I now known as Palmitoyl Tripeptide-1 in Matrixyl 3000™ and Biopeptide-CL, and Palmitoyl Hexapeptide-12 in Biopeptide-EL.
** Suppliers information. List of abbreviations: TGF: Transforming Growth Factor; RGD site: Arginine, Glycine, and Aspartate site; KMK tripeptide: Lysine-Methionine-Lysine tripeptide; EGF: Epidermal Growth Factor; GM-CSF: Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor; VEGF: Vascular Endothelial Growth Factor; HGH: Human Growth Hormone; IGF-1: Insulin-Like Growth Factor 1; TRX: Thioredoxin; TIMP-2: Tissue Inhibitor of Metalloproteinase 2; PER-1: Period Circadian Regulator 1; SNAP-25: Synaptosome Associated Protein; ACE: Angiotensin-converting Enzyme.

4. Discussion

This study explored the trending peptides used by the cosmetic industry in anti-aging formulations from the Portuguese market, which mainly encompasses multinational brands. From 2011 to 2018, the use of peptides in anti-aging products presented a small increase, reaching one fourth of the formulations on the market (Figure 1). However, the diversity of peptides almost doubled in these products, which reflects the growing importance of these ingredients in the period of analysis. The number of peptide combinations also followed this tendency. This observation may also be related with the use of peptide mixtures from ingredient suppliers, which often contain more than one peptide. There are 848 entries with the word "peptide" in the "European glossary of common ingredient names for use in the labelling of cosmetic products", but this study only identified 37 compounds, which corresponds to 4.4%. This may relate to the fact that this study is restricted to the anti-aging market and/or it may portray the lack of relevance of many peptides commercially available for cosmetic formulators.

In 2011, "Palmitoyl oligopeptide" was the most used peptide in cosmetic products, but this ingredient is hardly found in products released in 2018. This is possibly related to the fact that the term "Palmitoyl oligopeptide" was "removed" in 2013, as it has been used to designate two distinct molecules since its development in 1994. Those compounds were renamed as Palmitoyl Tripeptide-1 (Pal-GHK) and Palmitoyl hexapeptide-12 (Pal-KTTKS) in order to avoid misunderstandings. With this in mind, we found that the second most used peptide in 2018 was Palmitoyl Tripeptide-1, which demonstrates that this ingredient is still being used by formulators [40]. Curiously, the ingredient "Palmitoyl Oligopeptide" was still found in the composition of one product launched in 2018. Both matrikine-mimetic peptides act by stimulating fibroblast activity, thus increasing matrix protein and glycosaminoglycan synthesis in the dermis. Palmitoyl Tripeptide-1 has shown the ability to stimulate collagen synthesis in a human fibroblast culture and prevent its degradation after the exposure to UVA light [41]. Furthermore, Palmitoyl Tripeptide-1 has been tested in a clinical study involving 23 healthy female volunteers, at 4 ppm, promoting a small but statistically significant increase in skin thickness of about 4% [41]. Palmitoyl hexapeptide-12 is an elastin fragment used to stimulate collagen and elastin synthesis, as well as fibronectin and glycosaminoglycans. In a double-blind study, a group of 10 female volunteers performed two daily applications of an emulsion containing 4% Palmitoyl hexapeptide-12 or a placebo for one month. The application of the test product improved skin elasticity and firmness. However, the supplier did not provide the study methodology nor reported if these improvements had statistical significance [16].

The second most used peptide in 2011 was Palmitoyl Tetrapeptide-7, which in 2018 is ranking in first place. Palmitoyl Tetrapeptide-7 is a fragment of immunoglobulin G. Palmitoyl tetrapeptide-7 decreases IL-6 secretion and reduces inflammation after UVB exposure [42]. It is noteworthy that Palmitoyl Tetrapeptide-7 and Palmitoyl Tripeptide-1 are frequently used together in the ingredient Matrixyl™ 3000, which explains the usage percentages in 2018 [9].

Comparing the years 2011 and 2018, we found that the use of Acetyl Hexapeptide-8 (Argireline®, also known as Acetyl Hexapeptide-3), is starting to decline, as it was not found in new products released in 2018. Notably, Acetyl Tetrapeptide-5 is being used more frequently in 2018 compared with 2011 [15]. Although both peptides act by inhibiting neurotransmission, it is unlikely that this finding reflects a direct replacement, as Acetyl Hexapeptide-8 is used to reduce wrinkles and Acetyl Tetrapeptide-5 is directed to minimize the appearance of dark circles and under-eye bags. There are several clinical trials involving Acetyl Hexapeptide-8. The anti-wrinkle efficacy of this peptide was accessed in a placebo-controlled clinical study, where an oil-in-water (O/W) emulsion containing 10% Acetyl Hexapeptide-8 was applied twice a day on the lateral preorbital region of 10 healthy women volunteers. Silicon imprints were obtained after 0, 15 and 30 days and analyzed by confocal laser scanning microscopy. The analysis showed that the test product decreased the depth of skin wrinkles by 30%, whereas the placebo provided a 10% reduction [25]. Later, a placebo-controlled clinical study investigated the possible synergism between Acetyl Hexapeptide-8 and tripeptide-10

citrulline in a study involving 24 women. The use of 10% Acetyl Hexapeptide-8 topically, twice daily for 60 days, promoted a significant decrease in transepidermal water loss (TEWL) [43]. Contrary to Acetyl Hexapeptide-8, we were unable to find clinical studies supporting the topical use of Acetyl Tetrapeptide-5.

Even though the molecules Cyclotetrapeptide-24 Aminocyclohexane Carboxylate, Acetyl Dipeptide-1 Cetyl Ester, Tripeptide-1 and Dipeptide-2 appear in the top 12, no clinical studies supporting their use were found in the literature.

As for Acetyl Dipeptide-1 Cetyl Ester, there is no evidence for its use as an anti-aging ingredient. However, it may be useful to reduce skin irritation, as it has shown a soothing effect on the stinging/burning induced by a 40 ppm capsaicin cream [28].

Notably, in 2018, we verified the emergence of SH-Polypeptides, which are single-chain synthetic peptides produced by biotechnology in living cells, such as those from tobacco plant (*Nicotiana benthamiana*) leaves [43]. These peptides aim to mimic human growth factors and cytokines, thus stimulating cellular growth, proliferation and differentiation after their recognition by keratinocytes' receptors. In this study, all SH-Polypeptides found on the market were derived from *Nicotiana benthamiana*, and there was only one cosmetic brand using this technology.

This study also provides evidence that from 2011 to 2018, biotechnology has gained increasing importance over chemical synthesis, becoming the dominant source for obtaining peptides for the cosmetic industry. However, it is not possible to draw a definitive conclusion, since there is a relevant amount of peptides whose source is unknown.

Regarding peptides' mechanisms of action, we found that signal peptides were the most prevalent in both years, followed by neurotransmitter-inhibiting and carrier peptides. The greater use of signal peptides may be related to the fact that these ingredients have more scientific evidence supporting their efficacy [8]. Contrary to other categories, the use of neurotransmitter-inhibiting peptides has decreased by 42.2%. Enzyme-inhibiting peptides seem to be of low relevance in this market. There are not many studies supporting the efficacy of these peptides, which may be the reason for this finding [9].

By analyzing Table 1, it is noticeable that most peptides have molecular targets located in the skin dermis. Among peptides' multiple biomolecular inspirations, growth factors and components from the dermis extracellular matrix stand out.

Aside from market trends, the choice of active ingredients for formulating cosmetic products should also rely on their efficacy. The majority of clinical studies available were performed by ingredient suppliers in order to generate ingredients' claims and are not usually published in peer-reviewed publications. Furthermore, the methodologies used to perform those studies are often undisclosed. This practice may be due to commercial and competitive reasons. Consequently, the scientific evidence supporting the efficacy of peptides is scarce in the literature and the technical documentation available to formulators. Additionally, clinical studies comparing the efficacy of peptides with similar mechanisms of action are missing both in commercial and scientific references. Moreover, for many ingredients, we were unable to find any studies which could support their efficacy.

5. Conclusions

Peptides are relatively new ingredients in the cosmetics field, whose chemical and biological properties encourage the industry to continually develop innovative compounds. The trends in the use of peptides in the cosmetic industry were not reported up to this date. In this study, peptides incorporated in anti-aging cosmetic products from 2011 to 2018 were disclosed and a trend towards increased use was noted, reaching 25% of the anti-aging products from the studied market. The variety of peptides used and the number of products containing peptide combinations have nearly doubled. Considering their mechanism of action, signal peptides are the most used ingredients, followed by neurotransmitter-inhibiting and carrier peptides. Furthermore, most peptides lack randomized clinical studies demonstrating their anti-aging efficacy in scientific literature, and there is an absence of systematic reviews summarizing the results from the existing studies. The scarcity of independent and

peer-reviewed evidence regarding the efficacy of peptides in cosmetic products needs to be addressed by the industry and the scientific community. This may constitute a barrier for formulation scientists when developing effective anti-aging products and also for scientists involved in the development of new peptides. This study explored the trends related to the use of peptides in this market, mainly composed of multinational brands. Together, the growth of the anti-aging cosmetic market, the innovation potential from this field and the emergence of biotechnology may present as opportunities for scientists to develop new and more effective peptides.

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Limitations:: This study was performed for the Portuguese cosmetic market, which is dominated by multinational cosmetic brands. Therefore, this may result in discrepancies when comparing with other markets. This analysis focused solely on peptides with anti-aging activity, and thus, peptides with other effects were not included in the analysis. Many ingredients found in cosmetic products from the market lack scientific literature regarding their efficacy. Therefore, some of the information used in this study was collected in technical documents and patents from suppliers.

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