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Review

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Applications of bioactive peptides in cosmeceuticals: a review

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Abstract: The cosmetic sector is a multibillion-dollar industry that requires constant attention being paid to innovative product development and engagement. Notably, its market value is projected to exceed 750 billion U.S. dollars by 2025, and it is expanding as novel, climate-friendly, green, and sustainable components from natural sources are incorporated. This review is written based on the numerous reports on the potential applications of food-derived peptides while focusing on their possible uses in the formulation of cosmeceutical and skincare products. First, the production methods of bioactive peptides linked to cosmeceutical uses are described. Then, we discuss the obtainment and characterization of different anti-inflammatory, antimicrobial, antioxidant, anti-aging, and other pleiotropic peptides with their specific mechanisms, from various food sources. The review concludes with salient considerations of the cost of production and pilot scale operation, stability, compatibility, user safety, site-specificity, and delivery methods, when designing or developing biopeptide-based cosmeceutical products.

Key words: Cosmetic; Skincare; Bioactive peptide; Functional ingredient; Cosmeceutical

1 Introduction

Cosmeceuticals refer to cosmetic products that contain biologically active ingredients claiming to have drug-like benefits. The field of cosmeceuticals is dynamic. The corrective nature, decorative nature, and hygienic functions of cosmetics have recently made them popular worldwide. Based on this development, a common definition of cosmetics is that they are products that are applied to various human body parts, either orally or topically, to improve the protection of the body and its overall appearance (Aguilar-Toalá et al., 2019). The cosmetic sector is a multibillion-dollar industry that requires innovative product development and engagement. Notably, its market value is projected to be worth over 750 billion U.S. dollars by 2025 (Statista, 2023). It is currently expanding, as novel formulations are entering the market largely due to the use of biologically active compounds from natural sources and the ever-increasing demand of consumers for protective and therapeutic skincare products (Aguilar-Toalá and Liceaga, 2020; Fonseca et al., 2023). Users give priority to skin-friendly formulations with biofunctional molecules used in isolation or in mixtures. The products' potential benefits are derived from compounds and minerals like selenium, vitamins, primary and secondary metabolites of microbes, polyphenols, microbial and plant extracts, and hyaluronic acid, to effectively enhance or provide immunity, insulation or thermoregulation, and cellular protection (Wu et al., 2016; Alamgir, 2017; Dorni et al., 2017).

Reports repeatedly show that there are limitations to the use of biological molecules, including expensive production and certain side effects like allergenicity, irritability, and low potency, leading to the search for other functional ingredients that can overcome these barriers (Aguilar-Toalá et al., 2019). In this regard, bioactive peptides are known to be hypoallergenic, safer, and relatively inexpensive to produce (Ashaolu and Yupanqui, 2017; Ashaolu et al., 2017; Bhat et al., 2017; Beltrán-Barrientos et al., 2017; Hall et al., 2018). These peptides, which are short protein fragments purified and identified from protein hydrolysates, have been widely researched for their biological activities including anti-inflammatory, immunomodulatory, anti-cancer, antihypertensive, and

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antidiabetic effects, and have been incorporated into functional food formulations (Cicero et al., 2017; Kessler et al., 2019; Fernández-Tomé et al., 2023). The bioactive peptides used in cosmeceutical and skincare products are derived mainly from collagen. Collagen is regarded as the animal's most important extracellular protein, is responsible for protecting the mechanics of tissues and organs, and is popularly used as a green, safe, and natural material in multifarious sectors, including the pharmaceutical, tissue engineering, medical, food, and cosmeceutical industries (Ahmed et al., 2020). The collagen protein's primary structure is different from that of other proteins because it comprises about 35% glycine, about 10% hydroxyproline, and about 12% proline, all of which contribute to the positive effects of collagen-derived peptides on the skin, including increasing stratum corneal moisture content and improving skin viscoelasticity. (Maeda, 2018).

Bioactive peptides are short chains of amino acids (AAs) and have gained attention in the cosmetic industry due to their potential benefits for the skin. The peptides may stimulate collagen synthesis to provide anti-aging effects, improve skin elasticity, and reduce wrinkles (Lima and Pedriali Moraes, 2018). Some of them exhibit antioxidant properties, which aids in the neutralization of free radicals and protects the skin from oxidative stress (Shin et al., 2019; Muttenthaler et al., 2021), while others can contribute to the reinforcement of the skin barrier, thereby improving moisture retention and overall skin health (Yang et al., 2020). Certain bioactive peptides possess anti-inflammatory or wound-healing properties that help to soothe and calm irritated skin or accelerate wound healing by enhancing cell proliferation and collagen synthesis, respectively (Boshtam et al., 2017; Castañeda-Valbuena et al., 2022; Xu et al., 2023). This setting lays the foundation for exploring the potential of bioactive peptides sourced from food, not only for creating functional foods but also for developing pharmaceutical and cosmeceutical products. Therefore, this review considers the growing potential of food-derived bioactive peptides as novel functional ingredients in skincare and cosmeceutical products. The production methods of the peptides are described, followed by the different associated biological activities. Noteworthy issues to be considered when developing biopeptide-based cosmeceutical products are thereafter presented.

2 Methodology

Scopus, Web of Science, and PubMed are among the electronic databases used for the literature selection. Both published original and review papers focusing on peptides that are used in cosmeceutical applications were considered in the search. The search and selection procedures were conducted between July and October 2023, considering publications that span the past 15 years but putting more emphasis on the papers published most recently within the past 5 years. As several references were generated during the evaluation, their relevance was determined by examining the titles, abstracts, and keywords in each of them, including but not limited to "cosmetics," "cosmeceuticals," "skincare," "bioactive peptides," and "cosmeceutical peptides." About one hundred and forty selected articles were included after the screening.

3 Production of bioactive peptides

The obtainment and characterization of bioactive peptides from food sources involve several methods, including extraction, purification, and analysis techniques. The peptides are often derived from the hydrolysis of proteins using enzymatic or chemical methods (Wang et al., 2024). If not through these means, they can be produced by microorganisms during the fermentation of protein-rich substrates using microbial enzymes from organisms like *Lactobacilli* and Bacilli (Aguilar-Toalá et al., 2017; Alvarado Pérez et al., 2019; Akbarian et al., 2022). However, the most preferred choice of production based on control, speed, safety, and mildness, is enzymatic hydrolysis, whereby digestive enzymes or commercial proteases are used, including trypsin, corolase, alcalase, flavourzyme, Protamex, neutrase, pepsin, papain, and bromeline (Ashaolu et al., 2017). In this process, the parameters that must be controlled to generate the desired protein hydrolysates and subsequent peptides include the enzyme-to-substrate ratio, hydrolysis time, enzyme type, sequential or non-sequential use of enzymes, pH, and incubation temperature (Le et al., 2023b). To enhance the enzymatic process and the bioactivity of the generated peptides, certain pretreatments could be employed, including high-pressure,

ultrasonication, microwave-assisted enzymolysis, and microwave radiation (Le et al., 2023b).

Once the hydrolysates are obtained, purification techniques such as chromatography and ultrafiltration are employed. In this respect, high-performance liquid chromatography (HPLC) and other chromatographic methods are commonly used for peptide purification, while ultrafiltration techniques can be employed for the separation of peptides based on molecular weight (Ashaolu, 2020). The fractionation methods are used to separate, concentrate, and purify bioactive peptides. They also aid in the measurement of important parameters such as peptide charge and hydrophobicity (Ashaolu, 2020). Some researchers used electromembrane fractionation by electrodialysis with ultrafiltration and gel filtration chromatography (Suwal et al., 2018; Durand et al., 2019; Fontoura et al., 2019). After fractionation, bioactivity screening, peptide identification by sequencing or de novo synthesis, characterization, and bioactivity confirmation are conducted using applicable techniques and novel strategies. To characterize the peptides, for instance, mass spectrometry (MS) or nuclear magnetic resonance (NMR) could be used. MS is a powerful tool for determining the molecular weight and sequence of the peptides, while NMR spectroscopy can provide information on the three-dimensional structure of peptides (Le et al., 2023a). A schematic illustration of this process is presented in Fig. 1.

Biological assays are afterwards used to determine the bioactivity of peptides, such as antioxidant, anti-inflammatory, or antimicrobial activity (Ge et al., 2023). This is followed by the use of bioinformatics or computational methods, which aid in the prediction of potential bioactive peptides within protein sequences (Ashaolu, 2020; Le et al., 2023b). Now that the methods for producing peptides have been described, the next focus is on those peptides that are specifically linked to cosmeceutical benefits. The available studies in this regard show that in vitro, in vivo (mostly in mice, Table 1), or in silico approaches have been employed to prove the potential of the peptides. The dearth of reports on human/clinical trials is worrisome, nonetheless.

4 Biopeptides linked to cosmeceutical applications

Several peptides (especially collagen peptides) obtained from multifarious plant and animal protein sources are known to promote skin exfoliation, wound healing, skin renewal, collagen synthesis, and skin elasticity, and to reduce the appearance of wrinkles (Norzagaray-Valenzuela et al., 2017; Song et al., 2017; Liu et al., 2018; Montalvo et al., 2019). The skin is delicate, is the largest organ of the body, and is quite susceptible to internal and external or environmental

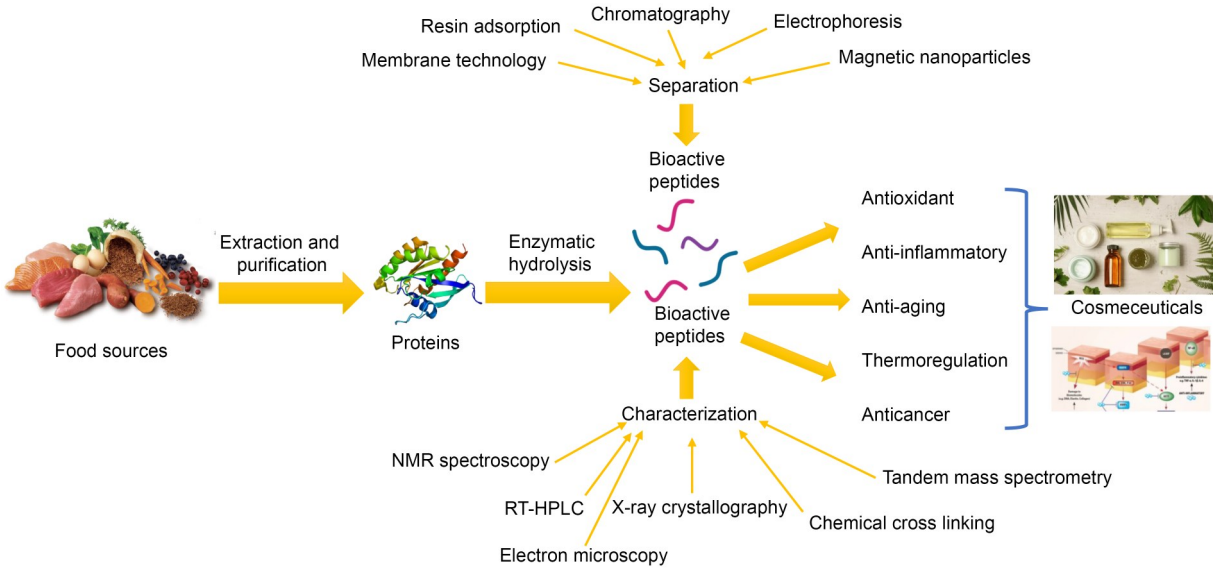

Fig. 1 Schematic illustration of the production of food-derived bioactive peptides that could be applied in the cosmeceutical industry. RT-HPLC: reversed-phase high-performance liquid chromatography.

Table 1 In vivo studies reporting the cosmeceutical potential of bioactive peptides upon oral administration

Bioactive peptide/ hydrolysate	Administration dose	Model used	Observation	Reference
Collagen peptide from *Tilapia zillii* scales	0.2 g/(kg·d) for 6 weeks	Hairless mice with skin damage by UV-B irradiation	The skin hydration increased, and epidermal hyperplasia reduced.	Tanaka et al. (2009)
Collagen hydrolysate from fish scale	Single dose: 20 mJ/cm^2 Repeated dose: 10–30 mJ/cm^2, 3 times/week for 6 weeks	Hairless mice with skin damage by UV-B irradiation	The stratum corneum water content increased, while the transepidermal water loss and epidermal thickness decreased.	Oba et al. (2013)
Pacific oyster (*Crassostrea gigas*) hydrolysate	Different doses of 35, 70, and 140 mg/kg for 9 weeks	Male C57BL/6 J mice with skin pigmentation by UV-B irradiation	The expression of MMPs, tyrosinase activity, and microphthalmia-associated transcription factor decreased.	Han et al. (2019)
Collagen hydrolysate from bovine skin	Hydrolysate consumption ad libitum for 4 weeks	Male Wistar rats	The MMP-2 activity decreased, but the expression of collagen types I and IV increased.	Zague et al. (2011)
Cos skin collagen peptides	50 and 200 mg/kg BW daily	Male ICR mice with UV-induced photodamage model	Overall immunity and antioxidant properties increased, while moisture, lipid, and glycosaminoglycans were maintained.	Hou et al. (2012)
Pacific cod (*Gadus macrocephalus*) skin collagen peptides	100 and 500 mg/kg BW daily	Female ICR mice with skin damage by UV irradiation	The MMPs and mitogen-activated protein kinases decreased, but the inhibitors of metalloproteinases increased.	Chen et al. (2016)
Collagen tripeptide	3.9 g daily for 12 weeks	Patients with atopic dermatitis	The eruption area, transepidermal water loss, and values of severity scoring of atopic dermatitis decreased.	Hakuta et al. (2017)
Fish and porcine collagen peptides (Peptan® F and Peptan® P)	10 g daily for 12 weeks	Placebo-controlled clinical trials	Skin hydration and dermal collagen density in the dermis increased, while fragmentation of the dermal collagen network decreased.	Asserin et al. (2015)
Three type I fish collagen peptides (Naticol® BPMG, Naticol® HPMG, and Naticol® 1000)	5 g daily for 8 weeks	Double-blind, randomized, and placebo-controlled clinical study	The wrinkles decreased, and skin firmness and elasticity increased.	Duteil et al. (2016)

UV-B: ultraviolet B; MMP: matrix metalloproteinase; BW: body weight.

aging factors; the ability of skin cells to proliferate and their biosynthetic capacity dwindle, thus causing senescence. The ultimate results of the aging process are loss of elasticity, wrinkle formation, blemishes, paleness, dryness, and rough or rugged texture (Limbert et al., 2019). Aging symptoms are characterized by a drastic loss of collagen, elastin, and hyaluronic acid, among other extracellular components of the dermis, contributing to oxidative damage, inflammation, disruption of the skin barrier, microbial colonization, and excessive moisture loss. In bad scenarios, acne, dermatitis, vasculitis, eczema, psoriasis, and skin cancer, among several other skin diseases, are triggered (Shin and Park, 2019).

The bioactive peptides used in the formulation of skincare products that target these crucial aspects of the dermal health status have been produced through conventional methods, such as enzymatic hydrolysis and well-established characterization techniques. The in silico studies use recent and novel techniques to screen peptides from various protein sources and match them with the right cutting proteases and specific bioactivities, to design their applications. The advantages of this novel approach include, but are not

limited to, the minimization of experiments based on peptides' structure–activity relationship, economics, and timeliness (Rani et al., 2018; Tu et al., 2018; Le et al., 2023b). It is also pertinent to note that, other than the use of in silico strategies, most studies conducted on the cosmeceutical applications of bioactive peptides are based on in vitro evaluations due to the cost-effectiveness of experimentation, ease of experimental performance, and the oxidative nature of most skin problems. For clarity and comprehensibility, the peptides linked to cosmeceutical applications are hereby split into anti-inflammatory, antimicrobial, antioxidant, anti-aging, and pleiotropic peptides. They are discussed in the following subsections.

4.1 Anti-inflammatory peptides linked to cosmeceutical applications

Infections and tissue injury are among the stimuli that cause inflammation. If inflammation is sustained for a long period and is uncontrolled, some pathophysiological conditions can be triggered. These conditions include rheumatoid arthritis, bacterial sepsis, and skin inflammation (Varma et al., 2019). In this regard, pro-inflammatory chemokines and cytokines associated with inflammation can be upregulated for an extended period. Inflammatory mediators play a significant role in the aging process, as they are produced in response to the internally and externally induced oxidative stress and impaired immunity that come with age. The inflammatory processes orchestrate multifarious cytokine factors using the macrophages and T-lymphocyte cells for the recruitment of leukocytes to the infection site. Immune regulatory molecules, such as interleukin-1α (IL-1α), IL-1β, IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), are inflammatory cytokines, whose levels could serve as biomarkers of inflammation (Maamar et al., 2022).

Therefore, it is common to evaluate the anti-inflammatory potential of food-derived biopeptides with assays that use these biomarkers or cell lines with lipopolysaccharides (LPS) to observe their anti-inflammatory mechanisms. The ability of peptides to bind lipid A moiety of LPS and interfere with LPS–cluster of differentiation 14 (CD14) interactions is key to understanding their anti-inflammatory action (Wang et al., 2020). In line with these pieces of information, egg yolk peptides (from α-, β-, and γ-livetin) reportedly show anti-inflammatory activity in LPS-induced RAW264.7 macrophages by inhibiting nitric oxide (NO), TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) production and expression, with respective peak values of 39.2%, 43.2%, 50.9%, 69.0%, and 62.0% (Meram and Wu, 2017). The peptides could inhibit the NO/iNOS and prostaglandin E2 (PGE2)/cyclooxygenase-2 (COX-2) pathways, and thus create an anti-inflammatory action. In a similar study using spent hen muscle protein rather than egg protein, out of seventeen anti-inflammatory peptides identified, the most potent was "FLWGKSY," which inhibited the production of IL-6 in endotoxin-activated macrophage-like U937 cells by 79% (Yu et al., 2018). This particular peptide from spent hen muscle could be used for anti-inflammatory cosmeceutical applications, as the tryptophan AA, known for its hydrophobic nature, is present in its sequence, which notably contributes to its inhibitory power and effect on IL-6.

Studies on milk and dairy-related peptides showed that β-lactoglobulin peptides have some anti-inflammatory potential after combining high hydrostatic pressure with proteolysis during their production (Bamdad et al., 2017). The peptides obtained with alcalase suppressed the production of NO and other pro-inflammatory cytokines in LPS-stimulated macrophage cells. Further sequencing of the peptides showed that 38% of their AAs are hydrophobic and aromatic residues (Bamdad et al., 2017). The study of another research group on the anti-inflammatory potency of whey peptides showed that the peptide "DQWL" is the most significant inhibitor of nuclear factor-κB (NF-κB) and p38 mitogen-activated protein kinase (MAPK) signaling pathways due to its inhibitory effects on IL-1β and TNF-α secretion (Ma et al., 2016). The peptide blocked messenger RNA (mRNA) expression of *IL-1β*, *COX-2*, and *TNF-α* in LPS-induced RAW264.7 mouse macrophages (Ma et al., 2016). Table 2 describes the various anti-inflammatory, antimicrobial, and antioxidant peptides with potential cosmeceutical applications.

These studies from the available literature on anti-inflammatory peptides are useful for formulating products that could provide mechanistic support against inflammation. However, specific studies targeting dermal fibroblasts and skin-enhancing anti-inflammatory peptide-based formulations or cosmeceutical products are limited. One such study involved egg ovomucin peptides, which showed an anti-inflammatory effect on

Table 2 Some antimicrobial, anti-inflammatory, and antioxidant food-derived peptides with potential cosmeceutical applications

Protein source	Hydrolysate/bioactive peptide	Observed effects/activity	Reference
Antimicrobial			
Saccharina longicruris protein	TITLDVEPSDTIDGVK, ILVLQSNQIR, ISGLIYEETR, MALSSLPR, ISAILPSR, LPDAALNR, IGNGGELPR, QVHPDTGISK, EAESSLTGGNGCAK	Antimicrobial action against *Staphylococcus aureus*	Beaulieu et al. (2015)
Crocodylus siamensis protein	QAIIHNEKVQAHGKKVL	Antimicrobial action against *Escherichia coli*, *S. aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*	Lueangsakulthai et al. (2017); Zanutto-Elgui et al. (2019)
Bovine milk protein	Peptides generated by *Aspergillus oryzae* and *Aspergillus flavipes* proteases	Antimicrobial action against *Listeria monocytogenes*, *S. aureus*, *Salmonella enterica* Enteritidis, *E. coli*, and *P. aeruginosa*	Beaulieu et al. (2015)
Rice bran protein	Cationic peptides	Antimicrobial action against *Propionibacterium acnes* JCM 6473	Taniguchi et al. (2017)
Alfalfa RuBisCo protein	MDN, ELAAAC, LRDDF, GNAPGAVA, ALRMSG, RDRFL	Antimicrobial action against *Listeria innocua*	Kobbi et al. (2018)
Anti-inflammatory			
Spirulina protein	LDAVNR (686 Da), MMLDF (655 Da)	IL-8 produced by endothelial cells EA.hy926	Vo et al. (2013); Alu'datt et al. (2021)
Whey protein	DQWL	IL-1β, COX-2, and TNF-α, and the secretion of IL-1β and TNF-α proteins in LPS-induced RAW264.7	Suttisuwan et al. (2019)
Sunflower protein	YFVP, SGRDP, MVWGP, TGSYTEGWS	IL-1β	Velliquette et al. (2020)
Millet bran protein	VLER, WVGK, VVRP, VLLF, VALVR, LFGK, FGPK	TNF-α, IL-1β, PGE2	He et al. (2022)
Spent hen muscle protein	FLWGKSY	IL-6	Yu et al. (2018)
Bee pollen protein	KLRSRNLLHPT, TNGRHSAKKH	COX-2, IL-6, iNOS, TNF-α	Saisavoey et al. (2021)
Antioxidant			
Monkfish muscle protein	EWPAQ, FLHRP, LMGQW	The peptides showed antioxidant activity in a concentration-dependent manner	Chi et al. (2014); Hu et al. (2020)
Rainbow trout (*Oncorhynchus mykiss*)	Hydrolysate	The microwave pretreatment improved (P<0.05) the antioxidant activity	Ketnawa and Liceaga (2017)
Skate (*Raja porosa*) cartilage	FIMGPY, GPAGDY, IVAGPQ	The peptides showed antioxidant activity	Pan et al. (2016)
Antarctic Krill (*Euphausia superba*)	AEK, VEK, VEKT, AEKTR, IEN, VEKGK, LKPGN, IEKG, LQP, ATH, IEKT, IDSQ	Peptides showed high scavenging activity on $HO^{\cdot}$, $DPPH^{\cdot}$, and $O_2^{\cdot-}$	Wang et al. (2021)
Miiuy croaker (*Miichthys miiuy*) swim bladders	FPYLR, GIEWA	Lipid peroxidation	Zhao WH et al. (2018)

To be continued

Table 2 (continued)

Protein source	Hydrolysate/bioactive peptide	Observed effects/activity	Reference
Red stingray (*Dasyatis akajei*) cartilages	VPR, IEPH, LEEEE, IEEEQ	Peptides exhibited DPPH, hydroxyl, superoxide anion, and ABTS cation radical scavenging activity. IEPH showed the strongest reducing power and lipid peroxidation inhibition activity, but LEEEE showed the highest Fe^{2+}-chelating ability	Pan et al. (2019)
Cricket (*Gryllodes sigillatus*) protein	LEEQQQTEDEQQDQL, YLEELHRLNAGY, RGLHPVPQ	The antioxidant action of peptides increased after simulated gastrointestinal digestion	Hall et al. (2018)
Camel milk protein	LEEQQQTEDEQQDQL, YLEELHRLNAGY, RGLHPVPQ	Isolated peptides showed low toxicity and a high antioxidant effect on HepG2 cells. The peptides increase the expression of *SOD* and *CAT* genes in treated HepG2 cells	Homayouni-Tabrizi et al. (2017)
Sweet potato (*Ipomoea batatas* variety Mixuan 1) protein	Hydrolysate	<3 kDa fraction showed the highest activity compared to others	Zhang et al. (2014)
Whey protein	Hydrolysate	<3 kDa peptides showed high activity	Alvarado Pérez et al. (2019)
Canola meal protein	Hydrolysate	<1 kDa fraction showed the highest activity compared to others	Alashi et al. (2014)
Pinto bean (*Phaseolus vulgaris* cv. Pinto) protein isolate	PPHMLP, PPMHLP, PLPPHMLP, PLPLHMLP, ACSNHSPLGWRGH, LSSLEMGSLGALFVCM	<3 kDa fraction showed the highest activity compared to other fractions with higher molecular weight peptides	Ngoh and Gan (2016)
Goat milk whey and casein	Hydrolysate	Fractions showed higher activity than their whole hydrolysates	Ahmed et al. (2015)
Bovine casein	Hydrolysate	<1 kDa fraction exhibited better activity than the 10 kDa fraction	Irshad et al. (2015)
Hen egg white lysozyme	NTDGSTDYGILQINSR	The isolated peptide showed both antioxidant and antimicrobial effects	Memarpoor-Yazdi et al. (2012)
Macroalgal *Palmaria palmata* protein	SDITRPGGQM	The peptide displayed the highest antioxidant activity	Harnedy et al. (2017)
Zein	Hydrolysate/M-I/L-P-P	Isolated tetrapeptide M-I/L-P-P displayed high activity	Wang et al. (2015)

RuBisCo: ribulose-1,5-diphosphate carboxylase/oxygenase; IL: interleukin; COX-2: cyclooxygenase-2; TNF-α: tumor necrosis factor-α; LPS: lipopolysaccharides; PEG2: prostaglandin E2; iNOS: inducible nitric oxide synthase; DPPH: 2, 2-diphenyl-1-picrylhydrazyl; ABTS: 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate); *CAT*: catalase; *SOD*: superoxide dismutase.

TNF-α-induced inflammation in dermal fibroblasts through the reduction of intercellular cell adhesion molecule-1 (ICAM-1) expression (Sun et al., 2016). Low-molecular-weight peptide fractions were obtained from ovomucin by the researchers, using alcalase enzyme potentate cosmeceutical applications that target dermal health maintenance and the treatment of skin diseases. Another similar study observed that collagen peptides derived from chicken had an anti-inflammatory effect on TNF-α-induced inflammation in dermal fibroblasts by downregulating the expression of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) (Offengenden et al., 2018). The peptides had distinct effects on inflammatory changes, oxidative stress, type I collagen synthesis, and cellular proliferation in human dermal fibroblasts. From these studies, it could be deduced that food-derived bioactive peptides may potentially be used as

anti-inflammatory functional ingredients in cosmeceutical and skincare products. Nevertheless, further validatory studies that employ cell lines of better specificity like the epidermal cells, as well as animal or human skin, are warranted.

4.2 Antimicrobial peptides linked to cosmeceutical applications

The body's defense mechanisms include intricate and external outmost barriers such as the skin, which provides the first line of defense against foreign or invading pathogens. It is therefore associated with an age-related decline in antimicrobial defense due to a lower production of cutaneous antimicrobial peptides that target pathogenic microbes (Kobayashi and Nagao, 2019). The microbial species known to cause a wide range of skin infections and diseases, such as acne vulgaris, atopic dermatitis, psoriasis, and rosacea, include *Propionibacterium acnes*, *Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (Niyonsaba et al., 2017; Pfalzgraff et al., 2018). These organisms might be inhibited or destroyed by precisely targeting them with antimicrobial biopeptides, which can be released as potent functional components of cosmeceuticals for topical applications.

Conventional treatments with antibiotics are effective, except that several of them are susceptible to resistance from some microbial strains over a certain period. For instance, *P. acnes*, which is responsible for acne vulgaris, has developed a resistant strain that conventional antibiotic treatments cannot deal with (Lim et al., 2015), making antimicrobial peptides a viable therapeutic alternative. The production of Alfalfa RuBisCo (ribulose-1,5-diphosphate carboxylase/oxygenase)-derived antimicrobial peptides, namely MDN, ELAAAC, LRDDF, GNAPGAVA, ALRMSG, and RDRFL, showed their mechanism of action against *Listeria innocua* through the irreversible disruption of the morphology and cell integrity of the bacterial cell membrane (Kobbi et al., 2018). Similar research showed that microalgal peptides, namely TITLDVEPSDTIDGVK, ISGLIYEETR, MALSSLPR, ILVLQSNQIR, ISAILPSR, IGNGGELPR, LPDAALNR, EAESSLTGGNGCAK, and QVHPDTGISK, derived from the hydrolysis of *Saccharina longicruris* protein, could exert antimicrobial action on *S. aureus* synergistically (Beaulieu et al., 2015). More examples of such antimicrobial peptides are provided in Table 2.

It is noteworthy that cationic peptides interact with the negatively charged membrane of microorganisms to cause the desired effects. For instance, rice bran cationic peptides demonstrated antimicrobial effects against tested human pathogens and fungi, specifically inhibiting *P. acnes* JCM 6473 effectively (Taniguchi et al., 2017). Using an in silico approach, cationic peptides generated from milk proteins through a virtual screening identification of antimicrobial peptides in the Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main. php) demonstrated an antibacterial effect upon performing antimicrobial assays (Liu et al., 2015). In another study, the peptide "QAIIHNEKVQAHGKKVL" was generated from the hemoglobin of *Crocodylus siamensis* (Lueangsakulthai et al., 2017). The cationic peptide, which is hydrophobic, showed antimicrobial effects against *E. coli*, *S. aureus*, *K. pneumoniae*, and *P. aeruginosa*, and permeated the microbial membrane, resulting in leakage and subsequent iron loss and cell death. These studies suggest the potential of food-derived peptides as functional ingredients in skincare formulations that could treat acne or other skin-related diseases; however, the mechanisms involved are still unclear and more studies are required to validate these claims.

4.3 Antioxidant peptides linked to cosmeceutical applications

Continuous exposure of the skin to ultraviolet (UV) rays leads to the production of reactive oxygen species (ROS) in excess, creating a reduction–oxidation disbalance and triggering oxidative stress associated with the pathophysiology of skin-related diseases (Kruk and Duchnik, 2014). Notably, photoaging could be promoted by the action of matrix metalloproteinase-1 (MMP-1) once ROS are generated from the UV impact (Leirós et al., 2017; Kim et al., 2018). Therefore, natural therapeutic antiphotoaging/antioxidant agents are necessary. In this regard, Chen et al. (2016) undertook a study to elaborate on the anti-photoaging mechanisms of gelatin peptides. The peptides derived from Pacific cod skin maintained the collagen content in photoaging skin by blocking the expression of MMP-1, MMP-3, and MMP-9 in photoaging skin, and increased tissue inhibitors of MMPs. In a later study, the peptide YGDEY showed a strong

inhibitory effect against ultraviolet B (UV-B)-induced photoaging in human keratinocyte (HaCaT) cells (Xiao et al., 2019).

Antioxidative biopeptides could serve cosmeceutical purposes by blocking or reducing oxidative stress in the skin based on their unique AA sequences, i.e., proline, histidine, cysteine, phenylalanine, tryptophan, and tyrosine (Han et al., 2019). These peptides have lower molecular weights, such as the <3 kDa peptide fraction generated by Ngoh and Gan (2016) from Pinto bean protein using the protease Protamex. From the fraction, six sequences, namely PPHMLP, PPMHLP, PLPPHMLP, PLPLHMLP, ACSNHSPLGWRGH, and LSSLEMGSLGALFVCM were isolated. These antioxidant peptides have potential applicability in the development of products that could be applied topically. The alcalase-prepared peptides from sandfish, especially ATSHH, also showed >66% radical scavenging capacity despite using various ionic concentrations, temperatures, and enzymes in a 2,2-diphenyl-1-picrylhydrazyl (DPPH) system (Jang et al., 2016). Similarly, peptides with antioxidant properties, such as those derived from marine sources, can protect the skin from oxidative stress. Wang et al. (2022) recently reported twelve antioxidant bioactive peptides from Skipjack tuna (*Katsuwonus pelamis*) by-products, including cardiac arterial bulbs, skins, scales, milt, roe, head, scales, and dark muscle. The peptides presented very strong DPPH, hydroxyl, and superoxide anion radical scavenging activity with additional high lipid peroxidation inhibition and ferric-reducing ability. The same group showed that the collagen peptides of Siberian sturgeon (*Acipenser baerii*) cartilages and monkfish swim bladders showed promising antioxidant capacities by decreasing ROS and malondialdehyde (MDA) contents (Hu et al., 2020; Sheng et al., 2022).

Antioxidant bioactive peptides have been produced from both fermented sheep and goat milk, in which <3 kDa fractions demonstrated stronger activity than higher-molecular-weight fractions (Aguilar-Toalá et al., 2017; Moreno-Montoro et al., 2017). There have been studies examining fractions lower than 3 kDa. For instance, canola (*Brassica* sp.) meal protein- and bovine casein-derived peptide fractions with <1 kDa showed the highest antioxidant activity compared with other fractions with higher-molecular-weight peptides (Alashi et al., 2014; Irshad et al., 2015). In these studies, it is evident that the hydrophobic nature of the peptides contributes to their antioxidant potential. In another study, the pentapeptides EWPAQ, FLHRP, and LMGQW were produced from *Lophius litulon* muscle protein, and were shown to possess good antioxidant activity (Chi et al., 2014). The peptides were released after the breakdown action of trypsin, and the observed activity followed a dose-dependent pattern. Later, some researchers also identified certain antioxidant peptides, such as LEEQQQTEDEQQDQL, YLEELHRLNAGY, and RGLHPVPQ, from camel milk protein, after pepsin-pancreatin sequential hydrolysis (Homayouni-Tabrizi et al., 2017). Similarly, peptic hydrolysates of goat milk whey and casein yielded peptides that demonstrated antioxidant effects (Ahmed et al., 2015). The use of the microwave-assisted enzymatic hydrolysis process on rainbow trout protein contributed immensely to the antioxidant activity of the peptide fractions generated in the process (Ketnawa et al., 2018). The activity was also measured after simulated gastrointestinal digestion. The peptides isolated from the higher antioxidant fraction of <1.8 kDa were sequenced and identified as NGRLGYSEGVM and GNRLGYSWDD. These peptides not only show antioxidant potential but also demonstrate antigenicity (Ketnawa and Liceaga, 2017). All these studies (with more examples in Table 2) show that smaller molecular weight peptides can be easily absorbed intestinally and circulated to produce the desired physiological effects in target tissues. These peptides also portend resistance to unwarranted in vivo enzymatic digestion. Cosmeceutically, the peptides can elicit antioxidant responses by suppressing photoaging-induced ROS in dermal tissues.

4.4 Anti-aging peptides linked to cosmeceutical applications

There are many studies showing the various bioactive peptides derived from yeast, snake venom, toads, and frogs, and from food sources like spirulina and rice, which have anti-aging potential in terms of reducing wrinkles and roughness in the skin and increasing skin firmness (Husein el Hadmed and Castillo, 2016; Zhmak et al., 2017; Negahdaripour et al., 2019). The target of the studies is often directed toward dermal cells (including collagen, hyaluronic acid, and elastin) and enzymes (including collagenase, elastase, hyaluronidase, and tyrosinase), since the cellular and

enzymatic complexes cause the gradual breakdown on the skin (Limbert et al., 2019). Once these enzymes are inhibited, anti-aging effects can be attained. Food-derived bioactive peptides could serve as anti-aging ingredients that target skin cells and prevent skin aging. Below is an overview of the inhibition properties of these bioactive peptides towards the main enzymes associated with skin aging. A description of various anti-aging studies that employ bioactive peptides is also presented in Table 3.

Table 3 Recently reported food-derived peptides shown to protect against skin aging

Peptide	Food source	Anti-aging effect	Reference
Type I collagen	Pig collagen	Enhancement of skin collagen content by changing the ratio of type I to type III collagen; no effect on skin moisturizing	Song et al. (2017)
High tripeptide-containing collagen hydrolysate (HTC-col) having high tripeptides comprising the Gly-X-Y sequence	Porcine skin	Anti-photoaging action; skin dryness improvement	Yazaki et al. (2017)
HGGEGGRPY, LQPSHY, and HPTSEVY	Rice	Tyrosinase inhibition	Ochiai et al. (2016)
LSPGDVLVIPAGYPVAIK, VESEAGLTETWNPNHPELR, EEYDEEKEQGEEEIR, and GPLVHPQSQSQSN	Faba bean (*Vicia faba*)	Tyrosinase inhibition	Karkouch et al. (2017)
Small peptides (<5 kDa) from soy milk fermented with lactic acid bacterial strains	Soy milk	Tyrosinase inhibition	Chen et al. (2013)
Chicken-derived collagen peptide	Chicken collagen	Anti-inflammatory activity; antioxidant activity; collagen I synthesis; improvement of cell proliferation on human skin fibroblasts	Offengenden et al. (2018)
YGDEY (Tyr-Gly-Asp-Glu-Tyr)	Tilapia collagen hydrolysate	Prevention of ultraviolet B (UV-B)-induced damage to cells; inhibition of UV-B-mediated photoaging of the skin; improvement of the glutathione and superoxide dismutase expression; enhancement of type I procollagen; reduction of the reactive oxygen species (ROS) in keratinocytes; prevention of DNA oxidative damage; inhibition of the collagenase and gelatinase expression	Xiao et al. (2019)
Ala-Tyr dipeptide	Carp skin hydrolysate	Antioxidant activity	Tkaczewska et al. (2019)
Hydrolyzed collagen	*Prionace glauca*	Stimulation of the collagen type I mRNA by fibroblasts; improvement of mRNA production	Sanchez et al. (2018)
Hydrolyzed collagen with neutrase	Alaska pollock	Antioxidant activity	Liu et al. (2018)
Hydrolyzed collagen with pepsin under acidic conditions	*Rana chensinensis*	Antioxidant activity	Zhao YY et al. (2018)
Hydrolyzed collagen with pepsin, subtilisin A, and both enzymes	*Arthrospira maxima* (spirulina)	Peptides obtained from PHS (peptide fraction with subtilisin A and pepsin) showed the highest collagenase inhibition activity	Montalvo et al. (2019)
Skin collagen peptides (3–10 kDa fraction)	*Todarodes pacificus*	Copper-chelation; anti-tyrosinase	Nakchum and Kim (2016)
Albumin peptide obtained using papain	Rice bran	Tyrosinase inhibition; copper-chelation	Kubglomsong et al. (2018)
Peptides from green microalgae species	*Tetraselmis suecica*, *Dunaliella tertiolecta*, and *Nannochloropsis*	Reduction of hyaluronidase enzyme	Norzagaray-Valenzuela et al. (2017)

Specifically, collagenase, elastase, hyaluronidase, and tyrosinase enzymes are responsible for degrading the core skin-enhancing components—collagen, elastin, hyaluronic acid, and tyrosine, respectively. The inhibition of these enzymes by food-derived bioactive peptides will support the integrity of the skin. For example, collagenase is responsible for degrading collagen, the most abundant protein and the primary structural component of the skin, providing flexibility, elasticity, and strength (Ramos-e-Silva et al., 2015). This degradation process is a typical phenomenon in the physiological human skin to maintain the firmness and elasticity of the skin, but the overproduction of MMPs and collagenase enzymes will drastically reduce the amount of collagen (Leirós et al., 2017). In light of this, food-derived peptides such as those isolated from spirulina and porcine skin collagen proteins have shown significant collagenase inhibition activity in vitro (Choi et al., 2018; Montalvo et al., 2019). Most of the peptides obtained have molecular weights that are less than 3 kDa. Likewise, ex vivo and in vivo evaluations of the peptides' potential to inhibit the MMPs, collagenase, and elastase of the dermis have been conducted using <1 kDa keratin peptide fraction (Jin et al., 2018), Pacific cod skin gelatin peptides (Lu et al., 2017), and <1 kDa peptides isolated from spent hen feathers (Yeo et al., 2018). Apart from inhibiting MMP-1 and MMP-13 expression in human and mouse dermal fibroblasts, the peptides could modulate histone modification and influence the MAPK and NF-κB signaling pathways, as well as the activation of phosphorylated extracellular signal-regulated kinase (p-ERK) and phosphorylated p38 MAPK. The murine and rat studies of the anti-aging effects of food-derived peptides obtained from Pacific cod skin gelatin and food-grade collagen showed their suppressive effects on the MAPK signaling pathway, inhibitory effects on MMPs, and increased levels of the tissue inhibitors of MMPs (Zague et al., 2018). These studies support the theoretical claim that collagen peptides isolated from food sources can serve as active components of cosmeceutical formulations to treat and prevent skin aging.

Elastase is an enzyme that degrades elastin, the protein that confers elasticity and flexibility to the skin and vital tissues. The production of elastin halts once the human body reaches maturity, due to the excessive production of elastase and the decrease in mechanical tissues (Kristensen and Karsdal, 2016; Leirós et al., 2017). Collagen and microalgal peptides from food sources have reportedly shown significant inhibitory effects on elastase (Norzagaray-Valenzuela et al., 2017). Although the studies showed that these peptides have the potential to enhance skin health, more studies on this claim are required. The hyaluronidase enzyme is known to inhibit the production of hyaluronic acid or hyaluronan when overproduced. This skin component can retain skin moisture, thereby contributing to viscosity, extracellular fluid permeability, and rejuvenation (Saranraj and Naidu, 2013; Garg, 2017). Several topically applicable cosmetic products have hyaluronic acid on their labels; nevertheless, it has been linked to inflammation (Saranraj and Naidu, 2013). Alternative measures to stop the breakdown of hyaluronic acid are warranted to protect the skin, and peptides obtained from microalgal proteins have shown this potential by inhibiting hyaluronidase (Norzagaray-Valenzuela et al., 2017; Montalvo et al., 2019). Another study focused on the potential of alcalase-generated squid collagen peptides to inhibit hyaluronidase and showed that the effect was molecular weight-dependent in fractions ranging from <1 kDa to >30 kDa (Nakchum and Kim, 2016). Surprisingly, unlike other related studies where the lowest fractions usually exert the highest inhibition rate, the 3–10 kDa fraction exhibited the highest hyaluronidase inhibitory activity at 32.21%.

Regarding the tyrosinase enzyme, its major effect on the skin is to inhibit melanin. Melanin is solely responsible for the skin color and could become degraded once tyrosinase is overproduced, thus leading to hyperpigmentation of the skin characterized by irregular gray patches on the face, neck, and trunk, as well as light to dark brown spots and pale brown to dark brown spots on the skin (Taofiq et al., 2016; Aguilar-Toalá et al., 2019). The tyrosinase enzyme has copper in its active site, which catalyzes oxidation reactions. Biopeptides that can block its active site or have copper-chelating potential would be useful for enzyme inhibition. Examples include squid skin collagen and rice albumin peptides, which showed both copper-chelating and tyrosinase inhibitory potentials (Nakchum and Kim, 2016; Kubglomsong et al., 2018). The rice protein-derived peptides, namely HGGEGGRPY, LQPSHY, and HPTSEVY, also demonstrated anti-tyrosinase activity, with one of them (LQPSHY)

using its C-terminal tyrosine residue to bind the copper-containing active site of tyrosinase (Ochiai et al., 2016). Other than the squid skin collagen peptides, various food-grade collagen peptides have also shown tyrosinase inhibition (Choi et al., 2018). Lastly, peptides isolated from faba bean protein were shown to inhibit tyrosinase based on their AA hydroxyl groups and the hydrophobic and aliphatic AA residues (Karkouch et al., 2017). The anti-aging potential of inhibiting these skin enzymes is crucial to the cosmetic and skincare industries.

4.5 Pleiotropic peptides with cosmeceutical potential

Certain food-derived peptides could provide more than one biological effect that would benefit the skin. Examples include rice bran, quinoa, amaranth, and chia seed peptides with angiogenic, antioxidant, antihemolytic, anti-inflammatory, and antimicrobial activities (Taniguchi et al., 2017; Mudgil et al., 2019; Urbizo-Reyes et al., 2019). In murine studies whereby collagen peptides were administered daily to hairless or UV-induced skin-damaged mice through oral gavage for six weeks, the peptides not only decreased the epidermal hyperplasia, skin barrier abnormalities, and skin elasticity dysfunction but also improved skin hydration (Tanaka et al., 2009; Oba et al., 2013). Other than general knowledge about their antioxidant activity, skin barrier capacity, anti-inflammatory activity, antimicrobial activity, and inhibitory effects on aging enzymes, most of the biopeptides reported have not been well studied for their action mechanisms or protective capabilities. Some in vivo studies targeted oral application of the peptides, banking on their circulation in the blood and eventual impact on the skin (Watanabe-Kamiyama et al., 2010; Kawaguchi et al., 2012; Yazaki et al., 2017), while others concentrated on their topical applications to improve skin moisture and dermal collagen density, firmness, and elasticity, among other functions like the reduction of wrinkles (Asserin et al., 2015; Duteil et al., 2016; Hakuta et al., 2017).

5 Salient considerations

The development of biopeptide-based cosmeceuticals faces various challenges, encompassing scientific, regulatory, and practical considerations. Biopeptides may be prone to degradation and instability, affecting their efficacy in cosmetic formulations (Agyei et al., 2016). Ensuring that biopeptides penetrate the skin barrier and reach the target cells in sufficient amounts can be a significant challenge, creating a bioavailability and penetration problem (Chopra et al., 2023). Another salient point to consider is the efficacy and mechanisms of action of biopeptides, because understanding the precise mechanisms of action of biopeptides on skin cells and tissues is essential for demonstrating efficacy. Another noteworthy consideration is the various regulatory requirements for cosmetic products that may vary across regions and ensuring compliance with those regulations (Fosgerau and Hoffmann, 2015). These can make or break product development and marketing. Of all these challenges, the safety and allergenicity of food-derived peptides are more pronounced (Kelleher et al., 2022; Zaky et al., 2022). Therefore, ensuring the safety of biopeptide-based cosmeceuticals and minimizing the risk of allergic reactions are key concerns.

The cost of producing biopeptides for cosmetic applications may impact the overall cost-effectiveness of the final products, whereas consumer acceptance of biopeptide-based products may be influenced by factors such as perceived efficacy, texture, and fragrance (Purnamawati et al., 2017; Al-Haddad et al., 2020). While the production cost could be relatively cheap and economically feasible, transitioning from laboratory-scale production to large-scale manufacturing while maintaining product consistency can be challenging (Xia et al., 2016), considering that the cosmeceutical market is highly competitive and ever-changing. Staying abreast of emerging trends and consumer preferences becomes critical in this respect.

It is not all doom and gloom; the development of biopeptide-based cosmeceuticals presents numerous opportunities due to the unique properties and potential benefits associated with bioactive peptides. For instance, micro- and nano-encapsulation techniques are used to prepare microbiome-friendly peptides capable of industrial pilot-scale production. Corrêa et al. (2019) have demonstrated this by encapsulating whey peptides with liposomal phosphatidylcholine without losing their bioactivity after storage for one month. Therefore, advances in formulation technology allow for the design of biopeptide-based cosmeceuticals with improved skin penetration and targeted delivery.

Biopeptides, such as collagen peptides, can still be incorporated into cosmeceuticals to stimulate collagen synthesis, promoting skin elasticity and reducing the appearance of wrinkles (Asserin et al., 2015). The copper-chelating peptides have also demonstrated potential in promoting wound healing and tissue regeneration. Indeed, different food-derived biopeptides can be incorporated into personalized skincare formulations, catering to individual skin concerns and types. Currently, certain anti-aging peptides from snake venom, yeast, frog skin, toads, spirulina, and fish show inhibition of crucial enzymes, including elastase, tyrosinase, collagenase, and hyaluronidase, which are required to degrade the skin protein matrix (Dini and Mancusi, 2023). They are mostly under patent protection and are not limited to the venom-derived pentapeptide-3 (GPRPA), which decreases skin roughness and wrinkles, and the yeast-derived hexapeptide-11 (FVAPFP), which improves skin firmness (Shin et al., 2019; Castro-Jácome et al., 2021; Dini and Mancusi, 2023).

The growing consumer demand for effective and science-backed skincare products creates opportunities for the development and marketing of biopeptide-based cosmeceuticals. Lastly, collaboration among academia, industry, and research institutions could foster innovation in biopeptide research, leading to the development of novel cosmeceutical products.

6 Conclusions

This review has primarily focused on the different food-derived bioactive peptides that could potentiate skincare and other various cosmeceutical applications based on their antimicrobial, anti-inflammatory, antioxidant, and anti-aging capabilities, among other pleiotropic capacities. Despite the conventional and novel cutting-edge techniques used to produce these peptides, more efforts should be directed towards highly efficient protein extraction and analytical equipment to obtain the highest and purest yields. The scale of peptide production should also be optimized to attain industrial capacity that is easy to apply to cosmeceutical design. The delivery of the peptides in formulations and various functional forms targeting personal care products should be novel and advanced, for instance, using robustly tested and validated nano-delivery methods to ensure consumer safety. In this regard, physical and chemical properties, biocompatibility, stability, site-specificity, and biopeptide-loading capability of the final cosmeceutical product must be ascertained.

Author contributions

Tolulope Joshua ASHAOLU conceptualized and designed the study, performed the literature search, and wrote and edited the manuscript. The author has read and approved the final manuscript.

Compliance with ethics guidelines

Tolulope Joshua ASHAOLU declares that he has no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by the author.

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