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Review

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Applications of bioactive peptides in cosmeceuticals: a review

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Abstract: The cosmetics 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 be worth over 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, among others, when designing or developing biopeptide-based cosmeceutical products.

Key words: Cosmetics; Skincare; Bioactive peptides; Functional ingredients; Cosmeceuticals

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, be it orally or topically, to improve the protection of the body and its overall appearance and (Aguilar-Toalá *et al.*, 2019). The cosmetics 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 *et al.*, 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, among others, to effectively enhance or provide immunity, insulation or thermoregulation, and cellular protection (Wu *et al.*, 2016; Alamgir and Alamgir, 2017; Dorni *et al.*, 2017).

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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 come to mind as they are known to be hypo-allergenic, 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 are short fragments of proteins, purified and identified from protein hydrolysates, and have been widely researched for their biological activities including anti-inflammatory, immunomodulation, anti-cancer, antihypertensive, and 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 mainly derived from collagen. Collagen is regarded as the animal's most important extracellular protein, responsible for protecting the mechanics of tissues and organs, and is popularly used as a green, safe, and natural material in multifarious sectors including 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 as it comprises ~ 35% glycine, ~10% hydroxyproline, and ~12% proline, all contributing to the positive effects of collagen-derived peptides on the skin, from increasing stratum corneal moisture content to improving skin viscoelasticity, etc. (Maeda, 2018).

Bioactive peptides comprise 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 aid the neutralization of free radicals and protect 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 through the enhancement of 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. First, the production methods of the peptides are described, followed by the different biological activities that they are associated with. 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 procedure 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 The 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, time of hydrolysis, enzyme type, sequential or non-sequential use of enzymes, pH, and incubation temperature (Le *et al.*, 2023a). 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.*, 2023a).

Once the hydrolysates are obtained, purification techniques such as chromatographic 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 the measurement of important parameters like the peptides' charge and hydrophobicity (Ashaolu, 2020). Some researchers used electro-membrane 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 confirmation of bioactivity are conducted using the 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.*, 2023b). A schematic illustration of this process is presented in **Fig. 1**.

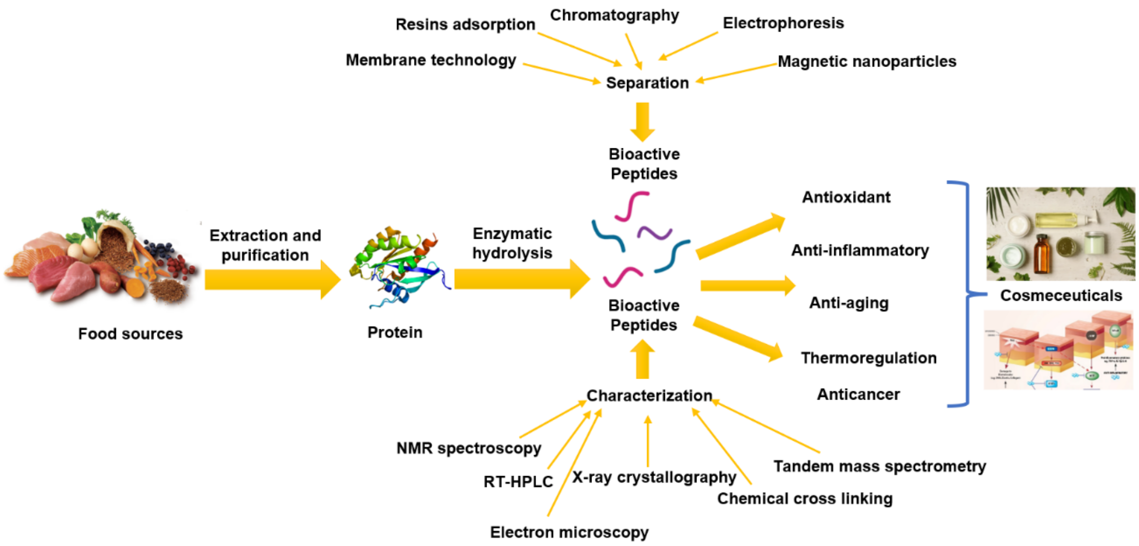

Fig. 1 Schematic illustration of the production of food-derived bioactive peptides that could be applied in the cosmeceutical industry

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.*, 2023a). 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, see **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.

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

Bioactive peptides/hydrolysate	Administration dose	Model used	Observations	References
Collagen peptide from *Tilapia zillii* scales	0.2 g/kg/d for 6 weeks	Hairless mice with skin damage by UV-B irradiation	Increase in skin hydration and reduced epidermal hyperplasia	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 decrease in MMP-2 activity but increased expression of collagen types I and IV	Zague *et al.* (2011)
Cos skin collagen peptides	50 and 200 mg/kg bw d	Male ICR mice with UV-induced photodamage model	Overall immunity and antioxidant properties increased while maintaining moisture, lipid, and glycosaminoglycans	Hou *et al.* (2012)
Pacific cod (*Gadus macrocephalus*) skin collagen peptides	100 and 500 mg/kg bw d	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, Naticol® 1000 MG)	5 g daily for 8 weeks	Double-blind, randomized and placebo-controlled clinical study	Decreased wrinkles and increased skin firmness and elasticity	Duteil *et al.* (2016)

MMPs: matrix metalloproteinases

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, 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 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, disintegrity of the skin barrier, microbial colonization, and excess 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 formulating skincare products that target these crucial aspects of the dermal health status have been produced through conventional methods vis-à-vis enzymatic hydrolysis *cum* 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.*, 2023a). 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 peptides, 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. The inflammatory mediators play a significant role in the aging process as they are produced based on the internally and externally induced oxidative stress and impaired immunity that come with age. The inflammatory processes orchestrate multifarious cytokine factors by using the macrophages and T-lymphocyte cells for the recruitment of leukocytes to the infection site. The immune regulatory molecules, such as interleukin (IL)1α, IL1β, IL2, IL6, IL8, IL12, tumor necrosis factor (TNF)α, and interferon (IFN)γ, are inflammatory cytokines, whose measurement 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 have these biomarkers or cell lines with lipopolysaccharides (LPS) to observe their anti-inflammatory mechanisms. The peptides' ability to bind LPS' lipid A moiety and interfere with LPS–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 RAW 264.7 macrophages by inhibiting nitric oxide (NO), TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (*i*NOS) production and expression, with interesting peak values of 39.2%, 43.2%, 50.9%, 69.0%, and 62%, respectively (Meram and Wu, 2017). The peptides could inhibit the NO/*i*NOS 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 contributed to its inhibitory power and effect on IL-6.

Studies on milk and dairy-related peptides show 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 shows that the peptide “DQWL” is the most significant inhibitor of nuclear factor kappa B (NF-κB) and p38 mitogen-activated protein kinases (MAPK) signaling pathways due to its inhibitory effects on IL-1β and TNF-α secretion (Ma *et al.*, 2016). The peptide blocked *m*RNA expression of IL-1β, COX-2, and TNF-α in LPS-induced RAW 264.7 mouse macrophages (Ma *et al.*, 2016). **Table 2** describes the various anti-inflammatory, antimicrobial, and antioxidant peptides that are of potential cosmeceutical use.

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*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*	Lueangsakulthai *et al.* (2017); Zanutto-Elgui *et al.* (2019)
Bovine milk protein	Peptides generated by *Aspergillus oryzae*, *Aspergillus flavipes* proteases	Antimicrobial action against *isteria monocytogenes* *Staphylococcus aureus* *Salmonella enterica* Enteritidis *Escherichia coli* *Pseudomonas 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) and 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 RAW 264.7	Suttisuwan *et al.* (2019)
Sunflower protein	YFVP, SGRDP, MVWGP, TGSYTEGWS	IL-1β	Velliquette *et al.* (2020)

Protein source	**Hydrolysate/bioactive peptide**	**Observed effects/activity**	**Reference**
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, *i*NOS, 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 activities on $HO^{\cdot}$, DPPH, and $O_2^{\cdot-}$	Wang *et al.* (2021)
Miiuy croaker (*Miichthys miiuy*) swim bladders	FPYLR, GIEWA	Lipid peroxidation	Zhao *et al.* (2018)
Red stingray (*Dasyatis akajei*) cartilages	VPR, IEPH, LEEEE, IEEEQ	Peptides exhibited DPPH, hydroxyl, superoxide anion, and ABTS cation radicals scavenging activities. 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, and RGLHPVPQ	The antioxidant action of peptides increased after simulated gastrointestinal digestion	Hall *et al.* (2018)
Camel milk protein	LEEQQQTEDEQQDQL, YLEELHRLNAGY, and 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	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, and 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	The <1 kDa fraction exhibited better activity than the 10 kDa fraction	Irshad *et al.* (2015)

Protein source	Hydrolysate/bioactive peptide	Observed effects/activity	Reference
Hen egg white lysozyme	NTDGSTDYGILQINSR	The isolated peptide showed both antioxidant and antimicrobial effects	Memarpoor-Yazdi *et al.* (2012)
Macroalgal *P. 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)

CAT: Catalase; SOD: Superoxide dismutase

These studies from the available literature on anti-inflammatory peptides are usable for formulating products that could provide mechanistic support against inflammation. However, specific studies targeting dermal fibroblasts and skin-enhancing anti-inflammatory peptides-based formulations or cosmeceutical products are limited. One such study involved egg ovomucin peptides, which showed an anti-inflammatory effect on 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 actions 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 skins, 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 targeting pathogenic microbes (Kobayashi and Nagao, 2019). The microbial species known to cause a wide range of skin infections and diseases like 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, *Propionibacterium acnes,* which is responsible for acne vulgaris, has developed a resistant strain that conventional antibiotics treatments cannot deal with (Lim *et al.*, 2015), making antimicrobial peptides a viable therapeutic alternative. The production of *Alfalfa* RuBisCo-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* in synergy (Beaulieu *et al.*, 2015). More examples of such anti-inflammatory 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, creating leakage and subsequent iron loss and cell death. These studies are suggestive of 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 is 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 gelatin peptides' anti-photoaging mechanisms. The peptides derived from Pacific cod skin maintained 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 UVB-induced photoaging in human keratinocytes (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 AAs' sequences, i.e., proline, histidine, cysteine, phenylalanine, tryptophan, and tyrosine (Han *et al.*, 2019). These peptides have lower molecular weights, like 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 1,1-diphenyl-2-picryl hydrazyl 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 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl, and superoxide anion radical scavenging activities 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 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 to the 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 activity observed 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 treatment enzymatic 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 felt 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 the dermal tissues.

4.4 Anti-aging peptides linked to cosmeceutical applications

There is a plethora of studies showing the various bioactive peptides from yeast, snake venom, toads, and frogs, and from food sources like spirulina and rice, among others, with 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, elastin, etc.) and enzymes (collagenase, elastase, hyaluronidase, tyrosinase, etc.), 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 targeting skin cells and preventing 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

Peptides	Food source	Anti-aging effect	References
Type I collagen-derived collagen peptide Chicken collagen	Pig collagen	Enhancement of skin collagen content by changing the ratio of type I and type III collagen. No effect on skin moisturizing.	Song *et al.* (2017)
High tripeptide-containing collagen hydrolysate (HTC-col) has 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)
Peptides	Faba bean (Vicia faba)	Tyrosinase inhibition	Karkouch *et al.* (2017)
Water and ethanol extracts from soy milk fermented with lactic acid bacteria strains,	Soy milk	Tyrosinase inhibition	Chen *et al.* (2013)
Chicken-derived collagen peptide	Chicken collagen	Anti-inflammatory. Antioxidant. Collagen I synthesis. Improve cell proliferation on human skin fibroblasts	Offengenden *et al.* (2018)

Peptides	**Food source**	**Anti-aging effect**	**References**
YGDEY (Tyr-Gly-Asp-Glu-Tyr) from.	Tilapia collagen hydrolysate	Prevention of ultraviolet (UVB)-induced damage to cells Inhibition of UVB-mediated photoaging of the skin. Improvement of the glutathione and superoxide dismutase expression. Enhancement of type I procollagen. Reduction of the 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.* (2018)
Hydrolyzed collagen	Prionace glauca	Stimulation of the collagen type I mRNA by fibroblasts. mRNA production improvement.	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 *et al.* (2018)
Hydrolyzed collagen with pepsin, subtilisin A, and both enzymes	Arthrospira maxima (spirulina)	Peptides obtained from PHS showed the highest collagenase inhibition activity	Montalvo *et al.* (2019)
Skin collagen peptides (3–10 kDa fraction)	Todarodes pacificus	Copper-chelation and anti-tyrosinase	Nakchum and Kim (2016)
Albumin peptide obtained using papain	Rice bran	Tyrosinase inhibition, copper-chelation	Kubglomsong *et al.* (2018)
Peptides	Tetraselmis suecica Dunaliella tertiolecta, and Nannochloropsis	Decrease in 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. Take collagenase, for example; it 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 matrix-metalloproteases (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; Hong *et al.*, 2019; 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 the inhibitory effects on MMP-1 and MMP-13 expression in human and mouse dermal fibroblasts, MAPK, NF-κB-signaling pathways, extracellular signal-regulated kinases (*p*-ERK), and phosphorylated *p*38 MAPK, the peptides could modify histone. 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 action on the MAPK signaling pathway, inhibitory effect on MMPs, and elevation of the tissue inhibitors of MMPs (Chen *et al.*, 2018; 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 diminishing 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 (Choi *et al.*, 2016; Norzagaray-Valenzuela *et al.*, 2017; Hong *et al.*, 2019). Although the studies showed that these peptides have the potential to enhance skin health, more studies on this claim are required. As for the hyaluronidase enzyme, it 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 in 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 that focused on the potential of alcalase-generated squid collagen peptides to inhibit hyaluronidase showed that the effect was molecular weight-dependent between fractions of < 1 kDa and >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 grey 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, meant to catalyze oxidation reactions. Biopeptides that can block its active site or that have copper-chelating potential would be useful in the enzyme's 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; Hong *et al.*, 2019). 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 cosmetics and skincare industry.

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 gavaging 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 (Duteil *et al.*, 2016; Asserin *et al.*, 2015; 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 action mechanisms 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 is a key concern.

The cost of producing biopeptides for cosmetic applications may impact the overall cost-effectiveness of the final products, while 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 a 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 between 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 optimizable to attain industrial capacity that applies to cosmeceutical design with ease. 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.

Abbreviations

Amino acids - AA
High-performance liquid chromatography - HPLC
Mass spectrometry - MS
Nuclear magnetic resonance - NMR
Interleukins - ILs
Tumor necrosis factor alpha - TNFα
Interferon gamma - IFNγ
Lipopolysaccharides - LPS
Cluster of differentiation - CD
Nitric oxide - NO
Inducible nitric oxide synthase - *i*NOS
Prostaglandin E2 - PGE2
Messenger ribonucleic acid - *m*RNA
Cyclooxygenase-2 - COX-2
Nuclear factor kappa B - NF-κB
Mitogen-activated protein kinase - MAPK
Intercellular cell adhesion molecule-1 - ICAM-1
Vascular cell adhesion molecule-1 - VCAM-1
Ultraviolet - UV
Reactive oxygen species - ROS
Matrix-metalloproteases - MMPs
Extracellular signal-regulated kinase - *p*-ERK
Human keratinocytes - HaCaT
2,2-diphenyl-1-picrylhydrazyl - DPPH
Malondialdehyde - MDA

Data availability statement

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Author contributions

Tolulope Joshua ASHAOLU conceptualized and designed the study, performed the literature search, wrote and edited the manuscript.

Compliance with ethics guidelines

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

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