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REVIEW

Overview of Peptides and Their Potential Roles in Skin Health and Beauty

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ABSTRACT

Peptides are molecules that consist of at least two amino acids linked by peptide bonds. The difference between peptides and proteins is primarily based on size and structure. Typically, oligopeptides consist of fewer than about 10–20 amino acids, and polypeptides consist of more than 20 amino acids, whereas proteins usually are made up more than 50 amino acids and often contain multiple peptide subunits as stated in the International Union of Pure and Applied Chemistry rules. Beyond the nutritional properties, peptides are also structural components of hormones, enzymes, toxins, and antibiotics and play several fundamental physiological roles in the body. Since the introduction of the first commercial peptide drug, insulin, peptide-based drugs have gained increased interest. So far, more than 80 peptide-based drugs have reached the market for a wide range of conditions, such as diabetes, cardiovascular diseases, and urological disorders. Meanwhile, peptides have also gained significant attention in the cosmetic industry because of their potential in boosting skin health. In this review, peptides were comprehensively summarized in the aspects of sources, function, the use of peptides in cosmetics and skin care, and indications for the delivery of cosmetic peptides.

1 | Sources of Peptides

1.1 | Endogenous Origin

Over the years, many bioactive peptides from animals, plants, marine creatures, and microorganisms have been characterized. The discovery of insulin opened the chapter for use of natural derived peptides as therapeutics. Except for intrinsic peptide hormones in human and animals, such as insulin, leptin, atrial natriuretic peptide, thyroxine, and melatonin, animal venoms are particularly attractive as they contain numerous peptides targeting a wide range of membrane channels, receptors, or enzymes [1]. Besides, peptides of animal origin, such as milk, egg, and meat, are ideal choices for obtaining bioactive peptides as they are rich in amino acids and proteins that have positive effects on the human body.

In addition, the marine environment is a treasure trove of natural products, including numerous bioactive peptides. With the discovery of over one million marine invertebrates and various species of fish, scientists have unearthed a wealth of natural compounds with potential biological activities. The purified marine peptides exhibit cytotoxic, anticancer, antioxidant, anti-inflammatory, anti-atherosclerosis, and antimicrobial properties, making them promising candidates for disease treatment. At present, a substantial number of marine-derived

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active substances or their derivatives (e.g., Ziconotide) have either received market approval or have entered clinical trials on a global scale. The structures and activities of bioactive peptides derived from marine sources vary significantly because of the diverse taxonomic groups, including fish, algae, bivalves, cephalopods, and crustaceans. Notably, these peptides exhibit enhanced resistance to enzymatic degradation in the gastrointestinal tract owing to their unique structural features [2].

Compared with animal peptides, plant peptides are composed of shorter chains of amino acids that are connected to create diverse structures, enabling them to exhibit a variety of biological function [3]. Plant-derived peptides are mainly extracted from dicot plants; therefore, their resources are more abundant and accessible than that of animal peptides. Bioactive peptides from plants are categorized into various families, such as ACE inhibitory peptides, cyclotides, defensins, glycinins, and plant knottins, based on their source, structure, or functional features. Proteins or peptides produced by plants or extracted from plants have some advantages over animal proteins, such as high economic benefits and lower immunogenic effects [4, 5]. However, plant-derived bioactive peptides inherently have drawbacks such as low chemical and physical stability, as well as a short plasma half-life.

It is well recognized that microorganisms have the capability to secrete a wide range of peptides that serve different functions during their life processes. One of the most notable examples is bacterial antimicrobial peptide (AMP) [6]. Additionally, during microbial fermentation, various proteases produced by microorganisms break down proteins, resulting in the generation of bioactive peptides.

Overall, endogenous produced natural peptides include ribosomally synthesized and posttranslationally modified peptides (RiPPs) and nonribosomal peptides. RiPPs are a major class of natural peptides generated by ribosomal peptide precursors, which will undergo posttranslational modifications (PTMs) to be fully activated. Apart from the discovery of endogenous RiPPs by bioassay-guided screening and genome mining, RiPPs engineering has proven to be a promising technology for creating RiPP analogs with improved properties. Techniques include rational design of sequence, site-directed mutagenesis, and incorporation of noncanonical amino acids. Because many RiPPs show potent biological activities, this renders them as ideal candidates for drug development [7, 8].

1.2 | Exogenous Origin

Except for endogenous production of peptides in various organisms, peptides can also be produced by chemical synthesis and biological synthesis. The most commonly used methods are solid-phase peptide synthesis, recombinant DNA technology, and enzymatic hydrolysis/fermentation [9–11].

Though peptides display several advantages over proteins and small molecules, such as specificity, selectivity, and safety, natural peptides are susceptible to enzyme degradation and have low membrane permeability. To overcome these limitations, various strategies have been applied to modify peptides. Because the composition of amino acids in a peptide determines its structure and activity, strategies such as backbone, side chains, or termini modifications are commonly used to improve peptide stability, permeability, and efficacy [12]. Natural peptides also teach us a lesson. For instance, cyclic peptides, in contrast to linear peptides, do not possess distinct N-terminus or C-terminus ends. The cyclic conformation renders the peptide chain more stable, and the decreased conformational flexibility also reduces the opportunity for the molecule to bind to proteolytic enzyme catalytic sites, resulting in improved protease resistance. Additionally, the cyclic structure facilitates its binding to membrane transport proteins, allowing for passive diffusion and active transport, thereby improving peptide absorption and membrane permeability [13, 14]. Therefore, cyclization of peptides through head to tail, backbone to side chain, and side chain to side chain are employed to achieve a better stability and permeability. Crosslinking of peptides by linkers, lactam-based bridges, disulfide bonds, or created chemical bonds are also used for this purpose [15]. Besides these, other approaches are also commonly used to modify peptides, including incorporation of noncanonical amino acids by genetic code expansion, conjugation of polyethylene glycol or fatty acid chains, and esterification [16].

On the basis of the advantages of peptide modifications, peptidomimetic drug development has evolved tremendously over the past few years. Peptidomimetics were developed in an attempt to mimic the structure and functionality of natural peptides while overcoming the drawbacks to transform peptides into drug-like molecules. Peptidomimetics can be designed through a variety of strategies, including modification of the backbone or side chains, introducing of unnatural components, and replacement of key residues/atoms by small molecules or functional groups. Peptidomimetics, compared with natural peptides, show higher stability, better bioactivity, and greater selectivity, making it highly promising as therapeutic agents [7, 17].

2 | Function of Peptides

2.1 | Signal Transduction

Peptide hormones and neuropeptides are abundantly produced in the endocrine and nervous systems and have been well recognized for their important roles in signaling transduction. They can act as signaling molecules by binding to receptors on targeted cells or tissues to regulate signaling pathways involved in development, metabolism, reproduction, and so on.

The physiological roles of peptide hormones and neuropeptides inspired the development of peptide drugs. Insulin was the first peptide hormone discovered by Frederick Banting and Charles Best in 1921. It was also the first peptide drug used for treatment of diabetes. Oxytocin and vasopressin were isolated and used clinically in the 1950s. With the development and application of new technologies, several bioactive peptides have been identified and studied [18]. At present, more than 80 peptide drugs are available in the pharmaceutical market, and a large part of them are developed based on peptide hormones and neuropeptides, such as gonadotropin-releasing hormone, growth hormone, somatostatin, semaglutide, and taltirelin.

Given the critical roles of peptide hormones and neuropeptides, research interest continues to grow in this field. To date, hundreds of peptide drugs are in clinical development or undergoing preclinical studies with the help of advanced peptide drug develop systems, including drug discovery, design, synthesis, modification, and evaluation.

2.2 | Cell Penetration

Cell-penetrating peptides (CPPs), also known as protein translocation domains (PTDs) or membrane translocation sequences (MTSs) [19], typically consist of 4–40 amino acids with hydrophobic or amphipathic character and usually are charged. They have the ability to cross cell membrane or tissue barrier without compromising their structural and functional integrity, making them excellent tools for facilitating the delivery of poorly permeable macromolecules across biological membranes. These macromolecules include oligonucleotides, nanoparticles, imaging agents, siRNA, drugs, proteins, and other peptides [20]. Direct cell membrane penetration and endocytosis are two major pathways suggested for the uptake of CPPs. Although the conjugation of drugs or molecules to CPPs greatly facilitates their transmembrane delivery, some types of CPPs are non-cell/tissue specific, such as cationic, hydrophobic, and amphipathic CPPs, and endosomal entrapment also limits the release of CPPs to the cytosol. To increase the cell specificity, screening CPPs selective for specific cells or tissues is particularly necessary. In addition, non-cell/tissue specific CPPs can be assembled with linkers as target peptides [21]. The cleavable linkers sensitive to specific enzymes or stimuli are used to trigger the internalization and release of CPPs, thereby enabling the cell-specific drug delivery [22]. For endosomal entrapment, selecting or designing CPP sequences with low affinity to the endosomal membrane, or oligomerizing CPPs, are the main strategies applied for endosomal escape [23].

Despite the significant amount of research and preclinical studies conducted so far, no CPPs or CPP/cargo formulations have been approved by regulatory agencies such as the EMA or FDA [24]. Several clinical trials have also been terminated without success. This is primarily due to issues related to stability, immunogenicity, potential cellular toxicity, and low specificity of CPPs. Nevertheless, several attempts have been made to exploit CPPs as a promising tool for delivery of therapeutic and cosmetic agents [19]. One skin-penetrating peptide, SPACE peptide, had been successfully used to enhance the topical delivery of hyaluronic acid (HA) in vitro in human skin and in vivo in mouse skin [25]. Further research is needed to optimize these properties and enhance the application potential of CPPs, such as modifying the sequence/structure, introducing of linkers, optimizing the charge of CPPs, and selecting suitable formulation for the CPP delivery systems.

2.3 | Antimicroorganisms

Most organisms produce AMPs, which are essential components of the innate immune system. AMPs can effectively combat various types of microbes, including bacteria, viruses, parasites, and fungi [26]. The structure of AMPs can take various forms, such as α-helices, β-sheets, extended structures, and loops. The mechanism by which they kill microorganisms depends on factors such as the charge, hydrophobicity, and structure of the AMPs [27]. The action of AMPs can be broadly categorized into two types. One involves membrane damage, such as targeting or formation of ion channels, formation of pores on the membrane, or extensive membrane rupture. Another mechanism involves targeting of intracellular events by inhibiting processes such as protein, RNA, and DNA synthesis, as well as enzyme activity [28]. In addition to the antimicrobial activity, AMPs also exhibit anti-insects, antipests, and anticancer activities. Their potential in combating drug resistance has endowed AMPs with a powerful ability against infectious diseases [29].

2.4 | Carrier

Peptides not only have multiple biological functions but can also serve as carriers for metal ions, radiopharmaceuticals, and cytotoxic drug delivery. Copper tripeptide-1 is primarily known as a carrier peptide that helps to stabilize and deliver copper into cells to boost skin health. To achieve targeted drug delivery, peptides can be conjugated with drugs to create cell-targeting peptides, which specifically deliver the drugs to cells expressing the corresponding peptide receptors. Tumor-homing peptides are peptides that can selectively bind to their receptors on tumor cells. The conjugations of cytotoxic drugs/imaging reagents to homing peptides show great potential in cancer therapy. Diagnostic radiopeptide tracers like octreotide and NeoTect are FDA approved, whereas radiolabeled somatostatin analogs, such as [111In-DTPA]-octreotide and [177Lu-DOTA(0),Tyr3]-octreotate, have shown promise in treating specific tumors [30]. Additionally, somatostatin analogs labeled with b1-emitters like 68Ga and 64Cu are used for tumor imaging with PET/CT scanners, aiding in patient diagnosis and evaluation [31]. As mentioned above, drugs conjugated to CPPs are also termed as peptide-drug conjugates (PDCs); however, for non-cell/tissue specific CPPs, a cleavable linker is required to achieve the specificity of CPPs. Taking the advantage of cell specificity and biological safety, homing peptides have been utilized to deliver imaging agents, drug molecules, and other therapeutic agents to tumors and diseased tissues [32]. Overall, PDCs have attracted significant research and development investment and are poised to have broader applications, such as cosmetic industry [21].

2.5 | Surfactants

Surface active agents are known for their ability to adsorb onto interfaces between fluids and solids and reduce the surface tension at these interfaces. These properties make surfactants indispensable in various applications in areas of pharmaceutical, food, and cosmetics industries. However, the synthetic surfactants commonly used in the composition of emulsions are known to exhibit toxic and irritant properties [33]. Natural surfactants have undoubtedly emerged as better alternatives. The most popular biosurfactants are lipopeptides.

Lipopeptides are composed of fatty acid moieties with varying degrees of branching and oxidation, linked to linear or

cyclic oligopeptides [34]. The nature of lipopeptides endows its application in the food and cosmetics industries. For example, replacing of lecithin with a lipopeptide surfactant at a concentration of 0.075% can lead to improvement in bread quality [35]. Strain *Nesterenkonia* sp. MS31, derived from the marine sponge *Fasciospongia cavernosa*, has the ability to produce lipopeptides with emulsifying capabilities. This property is highly valuable in the formulation and preservation of cosmetic products [36].

2.6 | Antioxidant Activity

Bioactive peptides exhibit strong antioxidant activity against free radicals and other reactive substances. By breaking the chain of free radical reaction and chelating metal ions, peptides can prevent enzyme-catalyzed and nonenzymatic oxidation. The antioxidant properties of peptides are mainly dependent on their composition and structure. The presence of certain amino acids and their positions in the peptide sequence have a significant impact on their antioxidant activity [37, 38]. Specifically, amino acid residues with the ability to form hydrogen bonds tend to exhibit higher antioxidant activity. The electronic properties of amino acids at the C-terminus also play a role, where greater electronic properties correspond to higher activity [39]. Moreover, basic and acidic amino acids, as well as other hydrophilic amino acids, when located at the N-terminus, exhibit higher activity compared with other amino acids. Compared with free amino acids, peptides have a higher antioxidant potential because of the unique chemical and physical properties conferred by the amino acid sequence itself [37]. Besides, the sequence and molecular weight of peptides also affects their antioxidant activity, which is attributed to their ability in acquisition and removal of free radicals [40].

Altogether, because of the multifunctional roles of bioactive peptides, they possess therapeutic effects in various diseases, including diabetes (insulin, insulin mimetics, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, etc.), cardiovascular diseases (natriuretic peptide, cenderitide, nesiritide, urantide, etc.), and gastrointestinal diseases (bombesin, linaclotide, plecanatide, teduglutide, etc.). Notably, in recent years, anticancer peptides have received enormous attention because of their specificity and low cytotoxicity. Anticancer peptides exert their effects through various mechanisms, such as membrane disruption, induction of apoptosis, tumor angiogenesis inhibition, immune modulation, and targeted inhibition of internal components. Taking advantage of tumor-homing peptides, PDCs enable the targeted delivery of therapeutic drugs or imaging agents to cancer cells, which is essentially useful for diagnosis, imaging, and treatment of cancer. Current anticancer peptides in clinics include peptides targeting GnRH receptors, growth hormone, and proteasome [41, 42].

Despite these functions, specific peptide sequences can serve as peptide vaccines targeting various diseases, including cancer, infectious disease, and Alzheimer's disease [43, 44]. Moreover, by incorporating bioactive peptides into edible films or food, it is possible to prolong the shelf life of food products while maintaining their desired sensory qualities and improving the flavor of food. In summary, bioactive peptides possess multiple functions, which lead to the application of peptides in medicine, food and beverage, and cosmetic industry. The discovery of new functions of peptides will further accelerate the application of bioactive peptides in various areas.

3 | Peptides in Cosmetics and Personal Care

In the pursuit of enhancing beauty, peptides have found an important place in the fields of cosmetics and personal care. One milestone in the history of peptide usage in skincare is the establishment of the anti-aging effect of palmitoyl pentapeptide-4 and palmitoyl dipeptide-7 in 2000s. Since then, many peptides have been developed and proven in their efficacy in skin care (Figure 1).

Among the over 8000 types of cosmetic ingredients currently included in the list by the National Medical Products Administration in China [45], peptides only account for about 3%. Nevertheless, among the newly registered cosmetic ingredients, application of peptides is continuously growing.

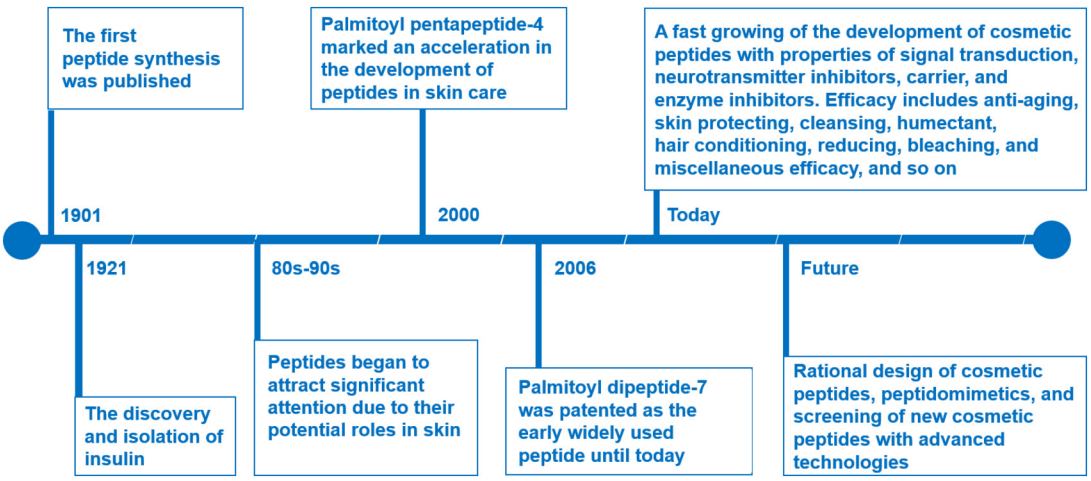

FIGURE 1 | Main timeline of peptides in cosmetics and personal care.

3.1 | Research Framework of Cosmetic Peptides

As the study of peptides progresses, it is found that peptides have extensive physiological activities in skin, including skin conditioning, skin protecting, cleansing, humectant, reducing, bleaching, antiaging, and miscellaneous efficacy [46]. Categorization using mechanism and efficacy is a prevalent method for peptides classification in cosmetics and personal care. A series of standardized models are used to validate the evidence of efficacy, such as in vitro cell/tissue culture experiments, animal experiments, and volunteer experiments. Fibroblasts, keratinocytes, melanocytes, skin explants, and organoids are wildly used in in vitro studies. The frequency of use is also a concern for relevant enterprises. Additionally, parent peptide molecules are often modified to improve the properties, such as efficacy, stability, and permeability. For example, acetylation and palmitoylation are commonly used methods to promote solubility and permeability of cosmetic peptides. Except for these aspects, systematic technologies and platforms for the development of novel peptides, establishing quality test and efficacy evaluation criteria as well as regulatory guiding principles are also crucial framework for cosmetic peptide development (Figure 2).

3.2 | Classification of Cosmetic Peptides

Cosmeceutical peptides are basically classified into three main categories, carrier peptides, signal peptides, and neurotransmitter-inhibiting peptides [47, 48]. Copper tripeptide-1 and its modified derivates are typical carrier peptides. Carrier peptides possess properties to stabilize and deliver unique ingredients, such as Cu(II) and Mn(II) [48–50] into cells to stimulate tissue repair. Because a few of carrier peptides, such as copper tripeptides, can act as both signal and carrier peptides, they are also considered as a subcategory of signal peptides by some researchers [51, 52]. The name of signal peptides derives from their ability to signal or mimic the signal involved in the synthesis of extracellular matrix proteins, skin cell turnover, and so on, thus modulating and enhancing skin health and beauty. For example, trifluoroacetyl-tripeptide-2, tripeptide-10 citrulline, palmitoyl tripeptide-3/5, palmitoyl tripeptide-38, palmitoyl pentapeptide-4, palmitoyl hexapeptide-12, acetyl tetrapeptide-9/11, and hexapeptide-14 are signaling peptides involved in extracellular matrix production. Hexapeptide-11 and tetrapeptide PKEK are signaling peptides involved in regulating senescence and skin whitening respectively. Among these peptides, palmitoyl tetrapeptide-7, palmitoyl hexapeptide-12, and tetrapeptide PKEK can also serve as anti-inflammation peptides, and acetyl tetrapeptide-11 and hexapeptide-14 can stimulate the proliferation of cells in skin [48, 51, 53]. Peptides termed neurotransmitter inhibitors with similar sequence to the synaptic proteins can potentially block the nervous responses, such as inhibiting the reaction of muscle cramps to reduce fine lines and wrinkles, thereby leading to a smoother skin. Pentapeptide-3, pentapeptide-18, and acetylhexapeptide-3 are such peptides with muscle relaxation properties [47, 48, 53]. Additionally, peptides with direct inhibitory effects on functional proteins should also be noted as peptide-based tyrosinase inhibitors have emerged as potential candidates for skin whitening [54].

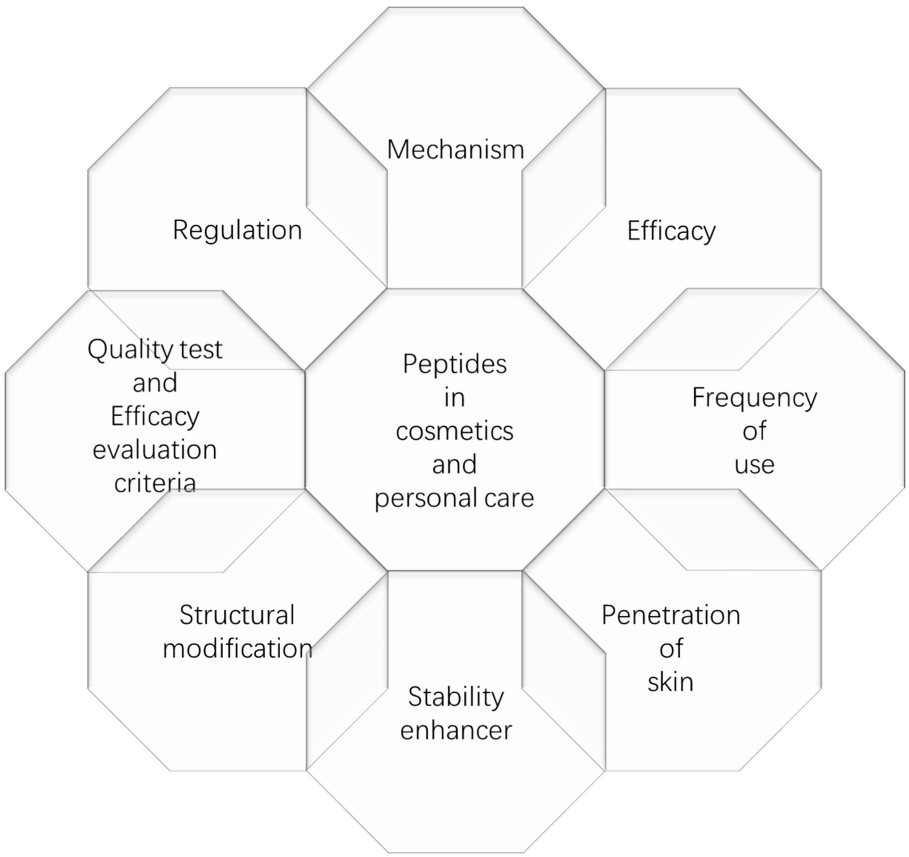

FIGURE 2 | Research framework of peptides for cosmetics and personal care.

3.3 | Extensively Used Cosmetic Peptides

A number of peptides are now commonly used in cosmetic industry. In order to promote access to the extensively used peptides for cosmetic application, the composition of a pool of peptides was collected from literature reviews or published works since 2018 (Table 1) [48, 55–58]. Only when the peptides reported are included in the official ingredient directories of both China [45] and the European Union [46], they were included in Table 1. The following is the description of some typical ones, which may provide valuable insight for the development of new and more effective peptide-based cosmetic ingredients. The structures of some commonly used cosmetic peptides discussed in this review are shown in Figure 3.

3.3.1 | Copper Tripeptide-1 and Its Derivates

Early researches and applications of copper tripeptide-1 largely involved contributions from Pickart. Pickart isolated copper peptides from human serum proteins in 1973 [59]. In 1980, Pickart discovered that copper tripeptide-1 may function by facilitating copper uptake into cells, by which it was classified into carrier peptide [60]. In 1982, Raju et al. discovered that copper tripeptide-1 could promote angiogenesis in rabbit corneas [61]. In 1983, Poole et al. discovered that copper tripeptide-1 acts as a chemotactic factor for mast cells and potentially associated with angiogenesis in tumor locations [62]. In 1985, Pickart et al. observed certain wound-healing and anti-inflammatory actions of copper tripeptide-1 [63]. A series of studies directed by Pickart et al during the late 1980s revealed more detailed mechanisms of copper tripeptide-1. These studies demonstrated tripeptide-1 could function independently to an extent comparable to copper tripeptide-1 in promoting collagen synthesis [64]. Of course, these findings do not contradict other functionalities that only copper tripeptide-1 could perform as a whole, such as acting as a transporter for copper ions in anti-inflammatory processes [65]. In addition, when tripeptide-1 is coupled with copper, tripeptide-1 silences the redox activity of copper, hence permitting the delivery of copper in a non-toxic form that can subsequently be utilized by the cells [61, 66–68]. Studies also indicated that copper tripeptide-1 enhance the collagen synthesis rate by neither altering the proline pool size nor reducing the intracellular degradation of procollagen [64].

Since the commercial use of copper tripeptide-1, a series of data on copper tripeptide-1 research have been accumulated on levels of in vitro cell and tissue culture, animal and volunteer studies, involving experiments on the aspects of imaging, tissue microscopy and ultramicroscopy, molecular detection, and gene expression. These provide the evidence for the main functions of copper tripeptide-1, which can now be encapsulated into four main categories: skin anti-aging, skin renewal, skin anti-inflammatory, and benefit in hair growth and transplants.

Serving as a bridge between peptides and skin care, copper tripeptide-1, even though it has been the subject of research and application exploration for more than half a century, still has not been fully exploited in the field of cosmetics and personal care because of multiple reasons including its high formulation application difficulty, among others. Regarding the fundamental research on the underlying molecular mechanism of copper tripeptide-1, there is still a lot of room for further investigation.

In addition, copper can be replaced by manganese. Topical application of manganese tripeptide-1 can significantly improves parameters associated with hyperpigmentation. [50] Besides, compared with tripeptide-1, biotinoyl/palmitoyl tripeptide-1, and biotinoyl copper tripeptide-1 show better efficacy. It was reported that biotinoyl tripeptide-1 is more stabilized and has the potential to reconstruct dermis by reactivation of stem cell niches in skin [69]. Palmitoyl tripeptide-1 stimulates collagen renewal, leading to reinforced skin and less wrinkles. Biotinoyl copper tripeptide-1 further facilitates the transportation of active components, copper, thereby promoting wound healing in rats [70]. Therefore, copper tripeptide-1 and its derivates can be explored further.

3.3.2 | Acetyl/Palmitoyl Peptides

As mentioned, modifying the structure of peptides with lipophilic group, in particular palmitoylation and acetylation, is a prevalent approach in cosmetics as lipophilic derivatives of peptides can increase the skin permeability.

For instance, palmitoyl pentapeptide-4 (pal-KTTKS) was detected in different skin layers (stratum corneum, epidermis and dermis), whereas pentapeptide-4 (KTTKS) was not observed in any skin layer under the same experimental conditions [71]. Decapeptide-12, a tyrosinase inhibitor, has low skin permeability. The conjugation of palmitate chain endows this molecular a lipophilic property, thereby increasing the transdermal delivery to efficiently regulate melanin production [72]. It is worth noting that palmitoylation modification also significantly increases peptide stability, preventing rapid degradation of peptides by enzymes in the skin. For example, upon entering the skin, pentapeptide-4 (KTTKS) is primarily degraded by aminopeptidases from the N-terminus [73]. As cyclic peptides are more resistant to enzymatic degradation owing to the lack of terminus exposure, palmitoylation may potentially protect the enzymatic cleavage sites at the N-terminus of the peptide. As expected, under the same experimental conditions simulating human body temperature, palmitoyl pentapeptide-4 (pal-KTTKS) exhibited lower degradation levels in both the dermal and epidermal layers compared with that of pentapeptide-4 (KTTKS) [71].

Another active peptide is acetyl dipeptide-1 cetyl ester, a synthetic lipopeptide composed of tyrosine acetate, arginine, and hexadecyl ester. It functions as a neurotransmitter-inhibiting peptide involved in regulation of muscle contractions [74]. Owing to the dipeptide Tyr-Arg, it provokes a rapid but fleeting suppression of pain by inducing the synthesis or the release of enkephalin in the brain [75, 76]. Nevertheless, the nonlipophilic dipeptide Tyr-Arg exhibits only slight activity as it can hardly penetrate the skin. To confer a better solubility and an increased power of penetration, a series of modifications were tested, and identified acetyl dipeptide-1 cetyl ester with significantly improved permeability [75]. Acetyl dipeptide-1 cetyl ester can signal the skin for relax by regulation of muscle contractions [74]. An explanation for this efficacy is that acetyl dipeptide-1

TABLE 1 | Peptides commonly used in cosmetic industry since 2018.

INCI name	Efficacy in CosIng	Description in CosIng
Di		
Carnosine	SKIN CONDITIONING	ND
Dipeptide diaminobutyroyl benzylamide diacetate	SKIN CONDITIONING	ND
Acetyl dipeptide-1 cetyl ester	HAIR CONDITIONING SKIN CONDITIONING	Tyrosine acetate and arginine, hexadecyl ester, dipeptide
Tri		
Tripeptide-3	SKIN CONDITIONING	Tripeptide-3 is a synthetic peptide containing glycine, serine and valine residues
Glutathione	REDUCING Changing the chemical nature of another ingredient by adding hydrogen (or removing oxygen)	ND
Palmitoyl tripeptide-1	SKIN CONDITIONING	Palmitoyl tripeptide-1 is the reaction product of palmitic acid and tripeptide-1
Palmitoyl tripeptide-5	SKIN CONDITIONING—MISCELLANEOUS (enhancing the appearance of dry and/or damaged skin by reducing flaking and restoring suppleness)	Palmitoyl tripeptide-5 is the reaction product of palmitic acid and tripeptide-5
Palmitoyl tripeptide-8	SKIN CONDITIONING	Palmitoyl tripeptide-8 is the product obtained by the reaction of palmitic acid and tripeptide-8
Trifluoroacetyl tripeptide-2	SKIN CONDITIONING SKIN PROTECTING	Trifluoroacetyl tripeptide-2 is the reaction product of trifluoroacetic acid and tripeptide-2
Tripeptide-10 citrulline	SKIN CONDITIONING	Tripeptide-10 citrulline is the reaction product of citrulline and tripeptide-10.
Biotinoyl tripeptide-1	HAIR CONDITIONING (enhancing the appearance and feel of hair. Leaving the hair easy to comb, supple, soft and shiny and/or imparting volume, lightness, gloss, texture, etc.)	Biotinoyl tripeptide-1 is the reaction product of biotin and tripeptide-1
Copper tripeptide-1	SKIN CONDITIONING	Copper tripeptide-1 is a copper complex of tripeptide-1
Tetra		
Tetrapeptide-21	SKIN CONDITIONING	Tetrapeptide-21 is the synthetic peptide consisting of glutamic acid, glycine, and lysine
Acetyl tetrapeptide-5	HUMECTANT (retaining and/or preserving the moisture in a product during use)	Acetyl tetrapeptide-5 is product obtained by the acetylation of tetrapeptide-5
Acetyl tetrapeptide-3	SKIN PROTECTING	Acetyl tetrapeptide-3 is product obtained by the acetylation of tetrapeptide-3
Palmitoyl tetrapeptide-7	SKIN CONDITIONING - MISCELLANEOUS	Palmitoyl tetrapeptide-7 is the reaction product of palmitic acid and tetrapeptide-7.

(Continues)

TABLE 1 | (Continued)

INCI name	Efficacy in CosIng	Description in CosIng
Penta		
Pentapeptide-3	SKIN CONDITIONING	Pentapeptide-3 is a synthetic peptide containing alanine, arginine, isoleucine, glycine, and proline
Pentapeptide-18	SKIN CONDITIONING	Pentapeptide-18 is a synthetic peptide consisting of alanine, glycine, leucine, phenylalanine, and tyrosine
Myristoyl pentapeptide-17	SKIN CONDITIONING	Myristoyl pentapeptide-17 is the product of the reaction of myristic acid pentapeptide-17.
Palmitoyl pentapeptide-4	SKIN CONDITIONING	Hexadecanoyl derivatives
Hexa		
Hexapeptide-2	BLEACHING (bleaching or lightening the shade of hair and/or skin) SKIN CONDITIONING	Hexapeptide-2 is a synthetic peptide containing Alanine, histidine, lysine, phenylalanine, and tryptophane hexapeptide
Hexapeptide-9	SKIN CONDITIONING	Hexapeptide-9 is a synthetic peptide containing glutamine, glycine, and proline residues
Hexapeptide-11	SKIN CONDITIONING	Hexapeptide-11 is a synthetic peptide containing Alanine, Phenylalanine, Proline and Valine residues
Acetyl hexapeptide-8	HUMECTANT (a substance added to skin cream to stop your skin from being dry) SKIN CONDITIONING	Acetyl hexapeptide-8 is the synthetic peptide consisting of arginine, methionine, and acetylated glutamic acid residues
Palmitoyl hexapeptide-12	SKIN CONDITIONING	Palmitoyl hexapeptide-12 is the product of the reaction of palmitic acid and hexapeptide-12
Octa		
Acetyl octapeptide-3	HUMECTANT SKIN CONDITIONING	Acetyl octapeptide-3 is the reaction product of acetic acid and octapeptide-3
Nona		
Nonapeptide-1	HAIR CONDITIONING SKIN CONDITIONING	Nonapeptide-1 is a synthetic nonapeptide derived from arginine, lysine, methionine, phenylalanine, proline, tryptophan, and valine

cetyl ester may promote the POMC (pro-opiomelanocortin) gene expression [74, 77]. POMC is the archetypal polypeptide precursor of hormones and neuropeptides [78], which can generate numerous biologically active peptides via a series of enzymatic steps, including β-endorphin, MSH (melanocyte-stimulating hormone), and ACTH (adrenocorticotropin), among which MSH and ACTH contribute to melanin synthesis [79]. Moreover, acetyl dipeptide-1 cetyl ester can enhance the efficacy of the epidermal barrier via significantly upregulating genes related to epidermal barrier [80].

As lipophilic derivatives of peptides show an amphiphilic character, they have the potential for self-assembly into a variety of aggregates. For example, the self-assembly of both palmitoyl pentapeptide-4 and palmitoyl dipeptide-7 has been reported. It has been demonstrated that the collagen stimulating behavior of palmitoyl pentapeptide-4 and its self-assembling behavior are correlated [81, 82]. As one of the earliest peptides used in cosmetics, palmitoyl pentapeptide-4 is still one of the most effective peptides in this field (Figure 1). In a clinical study reported in 2005, palmitoyl pentapeptide-4 achieved a variety of benefits,

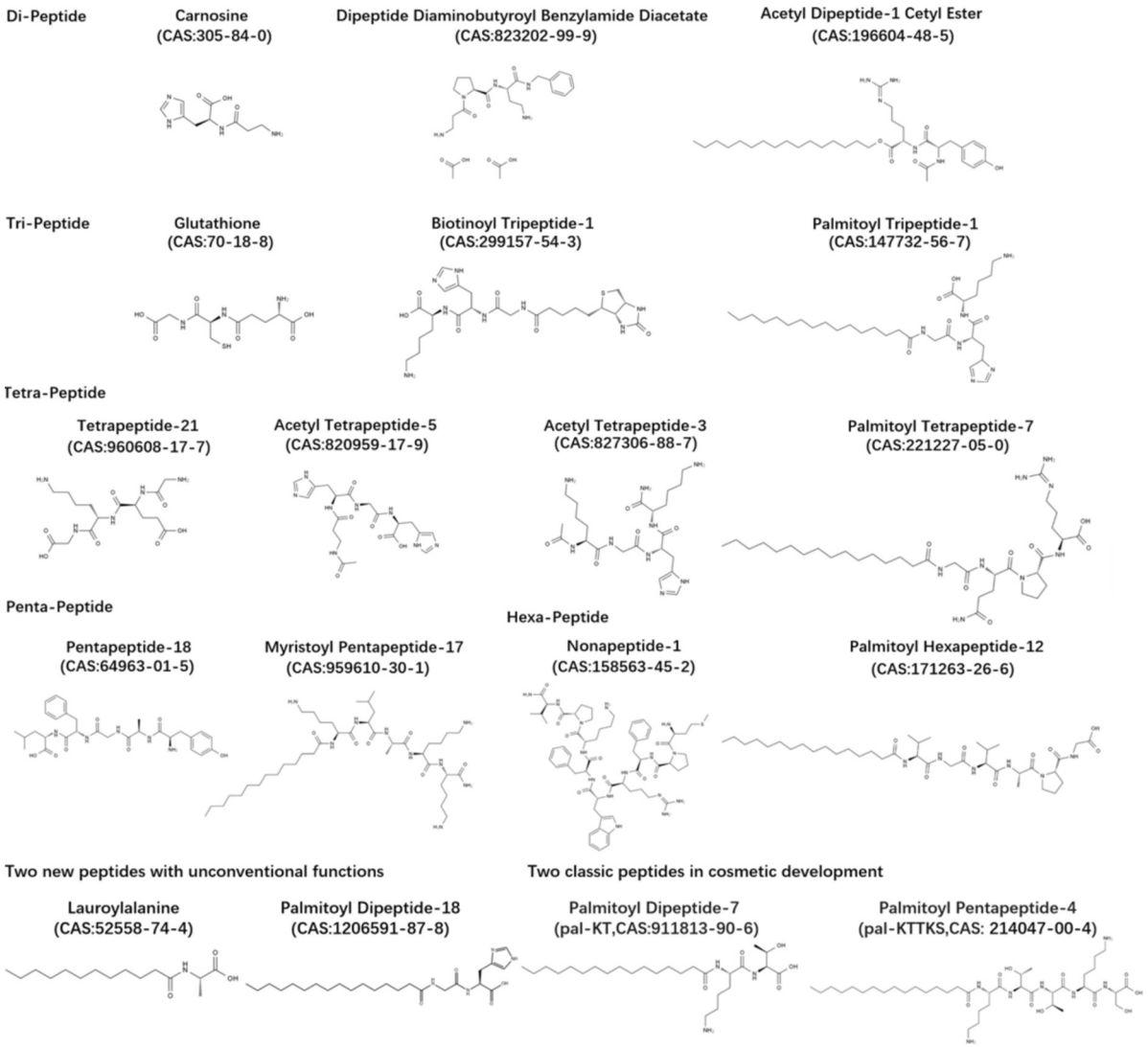

FIGURE 3 | The structures of some peptides discussed in this review.

including reducing wrinkles or fine lines [83]. To identify peptides with better anti-aging effects, a series of oligopeptides were synthesized and screened in vitro for evaluating their capacity in the 2000s. Among them, palmitoyl dipeptide-7 worked to the greatest extent [84]. Matrix effects of palmitoyl pentapeptide-4 and palmitoyl dipeptide-7 were demonstrated in 2009 and result in a better understanding of metabolic pathways in skin anti-aging [85]. In 2021, a combination of palmitoyl pentapeptide-4, acetyltetrapeptide 11, and niacinamide was found to activate nuclear factor E2-related factor 2-mediated oxidative stress responses in keratinocytes, which play an important role in the early stage of tissue repair. Meanwhile, a combination of palmitoyl dipeptide-7 and acetyltetrapeptide 11 was found to accelerate skin repair by synergistically restoring cellular ATP levels that had been depleted because of the presence of reactive oxygen species [86].

Moreover, it is observed that numerous R1-KXK (Lys-random amino acid-Lys)-R2 tripeptides are ineffective at the concentrations of a few ppm commonly found in cosmetics. Examples are palmitoyl tripeptide-5, Pal-Lys-Ala-Lys, and Pal-Lys-Ser-Lys. However, palmitoyl tripeptide-38, as a novel R1-KXK-R2 favored peptide, exhibits activity even at low ppm concentrations. Therefore, the composition and modifications are both critical for the functionality of a peptide [87]. In addition, other basic functions of lipophilic residues in cosmetics include softening, nutritional, and emulsifying [56, 88].

However, as lipopeptides exhibit amphiphilic property and antimicrobial activity, though lipopeptides are extensively used in cosmetics, the cytotoxicity of lipopeptides is a concern. It is well recognized that the high hydrophobicity of lipophilic moieties increases the cytotoxicity of lipopeptides. Neubauer et al. evaluated the chain lengths of lipids and properties of peptide backbones and observed that the chain lengths of lipids, the net charge, and the type of basic amino acids all contribute to the selectivity, activity, and cytotoxicity of lipopeptides [89]. Dawgul et al. found that the types and numbers of fatty acid chains involved in regulating the cytotoxicity of lipopeptides [90]. Moreover, because saturated fatty acids, compared with unsaturated ones, show less lipotoxicity, the saturation of fatty acid chains should also be considered [91]. Therefore, to reduce or eliminate the cytotoxicity, lipopeptides can be optimized by strategies such as improving the composition of the hydrophilic

and lipophilic moieties, refining the length, hydrophobicity, saturation, or number of the lipophilic chains, and selecting the appropriate concentration of application. Briefly, safety testing is required to guarantee the use of lipopeptides in cosmetics.

3.4 | Potential Sources of New Cosmetic Peptides

Owing to the advantages of peptides and the application of new technologies for peptides screening, modification, and synthesis, several bioactive peptides have been identified, synthesized, and extensively studied, and the use of peptides in cosmetic products increases dramatically in recent years. However, currently most cosmetic peptides are natural peptides or peptides modified/synthesized on the basis of the original structures. Therefore, the discovery of new types of peptides from natural sources are important.

N-Acetylneuraminic acid is a nonpeptide abundantly present in swiftlet's nest and is well recognized for its roles in multiple physiological and pathological processes. The study of N-acetylneuraminic acid can date back to the 1950s [92, 93]. Nonetheless, it was only in 2021 and 2022 that N-acetylneuraminic acid was filed by NMPA of China to be a new cosmetic ingredient with a range of applications, including anti-wrinkle, moisturizing, and antioxidation [94–96]. Of note, swiftlet nest peptide is actually a mixture of enzymatic hydrolysates of swiftlet nests [97]. The research on its active ingredients indicates a promising target for new cosmetic peptides [98]. Similarly, conotoxins contain abundant bioactive peptides from coin snails, which can target ion channels and neuron receptors of mammals, thereby providing another rich source of potential cosmetic peptides [99, 100].

For peptides with unconventional functions, lauroylalanine [101] and palmitoyl dipeptide-18 [102] were registered respectively in NMPA as cleansing and thickener in 2021 and 2022 by WEIMEI (Suzhou) and Nissan Chemical Corporation (Japan). Differing from traditional surfactants such as sodium dodecylbenzenesulfonate and sodium laureth sulfate, pure N-lauroyl-L-alanine, when used as a surfactant, exhibits excellent wetting, foaming, antimicrobial properties as well as resistance to erosion and static electricity [103]. Lauroyl sodium L-alaninate is a novel type of surfactant with PH closely resembling that of human skin. As a result, it shows low toxicity and non-irritating properties. This makes it a preferred ingredient in daily cosmetic items [104]. In CosIng, a European Cosmetic Ingredient Database, the efficacy of palmitoyl dipeptide-18 is denoted as viscosity controlling of cosmetics [46]. In summary, peptides show great potential in cosmetic industry based on their functionality and efficacy.

Furthermore, traditional medicine, wine, vinegar, and coffee also contain a series of bioactive peptides [105–107]. All these sources can be explored for potential new cosmetic peptides. In addition to glutathione, carnosine, and carcinine, which are cosmetic peptides used in early stages with antioxidation properties show several benefits to skin because of the ability to fight oxidative damage [108, 109]; hence, screening of new peptides with antioxidation potentials is also a future direction for cosmetic peptide discovery.

Taking advantage of advanced biotechnologies, peptidomimetics and de novo design of peptides are widely used in peptide drug development. Nonetheless, the development of cosmetic peptides lags behind. Palmitoylation, acetylation, and myristoylation are commonly used approaches for cosmetic peptides modifications. Other key approaches, such as incorporation of noncanonical amino acids, modification of backbones, and rational design of cosmetic peptides, are rarely applied. So far, biotinoyl tripeptide-1 is the only biotinoylated peptide that has been applied in cosmetic products. Despite the fact that hydroxyproline and its derivates have been widely used in cosmetic products, and some noncanonical acids, such as L-homoserine, N-hydroxyglycine, and N-hydroxyserine show great potential as moisturizing cosmetic additives [110], they have not been incorporated into cosmetic peptides. Because the system for peptide drug development has been well established, it definitely will pave the path for new cosmetic peptides development [111].

3.5 | The Indications for the Delivery of Cosmetic Peptides

Peptides have advantages over small chemical molecules in specificity and selectivity, but they often has poor ability to penetrate the skin. As mentioned above, improving transdermal permeability can be achieved through modifications of peptide functional groups or side chains to increase the lipophilic properties. Hydrophobic groups, such as lipophilic amino acids and fatty acids with varying chain lengths, have been strategically utilized to enhance the permeability of peptides. These modifications induce alterations in the distribution coefficient or influence the orientation of peptides within the lipid layers of the stratum corneum, thereby enhancing the permeability [72]. Among these modifications, palmitoylation stands out as the most prevalent method. A total of 89 INCI names containing the keywords “peptide” and “palmitoyl” were listed in the CosIng as of July 2022 [46].

Besides, methods employed for enhancing drug delivery can give us some indications for cosmetic peptides delivery. Microneedles, ablative, and nonablative fractional lasers are physical transdermal technologies that facilitate transdermal absorption of large biomolecular drugs by disruption of the stratum corneum. Though these methods are proven effective in delivering of drugs with diverse forms, the damage to the skin should be concerned. Low-frequency sonophoresis and iontophoresis are noninvasive methods. However, the properties of drugs, such as concentration, molecular weight, charge, or stability will influence the effectiveness of drug delivery. In addition, suitable devices are required for the application. Microemulsions showed great potential in delivering cosmetic peptides [112, 113], but the stability of the microemulsions is a problem. Other commonly used methods are skin penetration enhancers. Ionic liquids and chemical permeation enhancers (ethanol, fatty alcohols, etc.) are valuable for increasing drug skin permeability; nonetheless, their toxicity, selectivity for the delivery substrates, stability, and efficiency vary significantly.

As for transdermal peptides, CPPs are currently being used to develop cosmetics. Studies on the skin structure have suggested that the penetration potential of CPPs is based on the molecular interactions and characteristics of the lipid lamellar structure

between corneocytes in the stratum corneum [19]. Once drugs are conjugated to CPPs, they can be termed as PDCs. Certain kind of PDCs not only has advantages in skin permeability and easier chemical synthesis but also has advantages in tissue specificity by using the peptides or linkers to target specific tissues. Because of the target specificity of PDCs, utilizing PDCs to target different skin layers and cell populations to achieve different functions will become a key topic in the development of active ingredients for pharmaceuticals and skincare products, for instance, targeting skin aging–associated secreted proteins (SAASP) secreted by aged dermal fibroblasts to pinpoint aging cell populations, targeting the binding of the senescence-associated secretory phenotype (SASP) to attenuate the transmission of aging signals to the surrounding area [114], or targeting melanocytes in the basal layer of the skin to promote skin whitening. In addition to the well-known work by Chen et al. in 2006 [115], which successfully applied the epithelium-targeting peptide ACSSSPSKHCG for transdermal delivery of insulin, various target-specific peptides have been continuously studied and utilized [116], providing possibilities for the wide application of targeted transdermal delivery in pharmaceuticals and cosmetic skincare.

To mimic the property of nature membrane of cells, encapsulation of peptides using phospholipid-based vesicular systems like liposomes, niosomes, ethosomes, transfersomes, lipid-nanoparticles, or liquid crystal nanoparticles can also enhance the skin permeability of loaded substances. For these vesicular systems, liposomes are one of the earliest successful systems in the cosmetics industry [117]. Today, the diverse delivery systems based on liposome remain a hot topic in new cosmetic research. Strategies are developing to improve the drawbacks of vesicles, such as aggregation and fusion of vesicles, drug leakage, or degradation of encapsulated drugs. Despite the use of phospholipid-based vesicles, microspheres exhibit sustained release capability and specific affinity with certain cells or tissues, allowing the targeted and prolonged drug delivery [118]. Hydrogels not only preserve the skin moisture by capturing water, but also offer emollient properties to facilitate the drug delivery. Nonetheless, these delivery systems are not suitable for all peptides [119–122].

Overall, there are no dedicated techniques for peptides delivery. To improve the transdermal permeability of cosmetic peptides, the combination of some techniques holds significant potential to enhance the peptides delivery, such as the combination of laser-induced microchannels and phospholipid-based vesicular systems. The property of the peptides should also be considered to ensure a most appropriate delivery strategy.

4 | Conclusion

Bioactive peptides were brought into attention since the discovery of insulin. At the beginning of the 20th century, researches mainly focus on the natural peptide hormones derived from human. In fact, it is the therapeutic roles of these peptide hormones initiated the field of peptide drug development.

With the increase of research interest, numerous bioactive peptides have been identified and isolated from different species, ranging from microorganisms to vertebrates. Among them, many bioactive peptides show powerful therapeutic properties. Nowadays bioactive peptides are widely used in medicine, food and beverage, cosmetics and personal care owing to their multifaceted roles, such as signal transduction, anti-microorganisms, antioxidation, cell penetration, surfactant-like, drug-conjugation, and cell-targeting properties. The application of new technologies in the production and modification of bioactive peptides further accelerates the development of peptides industry. To overcome the inherent disadvantages of natural peptides, modification of natural peptides or production of peptides mimicking natural peptides are commonly used to improve their stability, permeability, safety, and activity. Aiming to get peptides with desired properties, peptides can be designed or modified to meet the criteria. In recent years, advances in bioinformatics further facilitate the design and modifications of peptides, rational design of peptides is a trend of future. Additionally, the development of efficient peptide delivery strategies is also essential for the application, especially in cosmetic industry. As we mentioned above, though the development of cosmetic peptides is slower than that of peptide drugs, considering the important physiological roles of bioactive peptides in skin, and their advantages over small chemical molecules, we expect that the cosmetic peptides market will continue to grow and attract more investments.

Author Contributions

Conceptualization: Z Zhang, L Zhang, and XL Wang. Writing: Z Zhang, L Wang, Z Wu, and XY Wang. Advice from cosmetic point of view: XL Wang, J Mao, L Zhang, and Y Yan.

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Conflicts of Interest

Lu Zhang, Xiaoli Wang, Jingzhuo Mao, and Yan Yan are employed by The Procter & Gamble Company. Zhuzhen Zhang, Leyang Wang, Zhijing Wu, and Xinyu Wang state no conflict of interest.

Data Availability Statement

No datasets were generated or analyzed during the current study.

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