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Collagen peptides and the related synthetic peptides: A review on improving skin health

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ABSTRACT

With the emergence of social aging problem, people's demand for active ingredients for skin health protection and therapeutic efficacy increases. Bioactive peptides are the optimal substances for skin anti-aging with its great diversity of biological activities and high security, such as antioxidation, anti-aging, anti-diabetes, anti-hypertension, and antibacterial. In recent years, natural and synthetic anti-aging peptides have been extensively studied *in vitro*, *in vivo* and clinically. Anti-aging peptides, such as collagen peptides, can affect various physiological pathways of skin, and have significant skin protection effect when applied locally and eaten. These characteristics show that bioactive peptides can improve skin health by providing specific physiological functions. In this review, we summarized the research of anti-aging peptides and the finishing of anti-aging peptides on improving skin health which is mainly based on the collagen peptides and the related synthetic peptides.

1. Introduction

Bioactive peptides, as natural antioxidant active peptides, have been widely recognized for its positive effects on human body in recent years. The extraction of bioactive peptides from food or other natural substances has been researched and reported largely around the world. Bioactive peptides are linear or cyclic polymers composed of amino acids that are covalently linked by peptide bonds in different combinations and arrangements. Commonly, bioactive peptides include both oligopeptides and polypeptides. The former consists of 2–20 amino acids and more than 20 are called polypeptides (Karami and Akbari-adergani, 2019). Bioactive peptides are inactive specific protein fragments in parent proteins that have positive functions and benefits to the human body after being released such as anti-diabetes, anti-hypertension, and antibacterial activity (Ogori et al., 2019).

As the emergence of aging population and the healthy consciousness gradually deepens, people pay more attention to their skin health. A series of bioactive compounds, such as plant extracts (Ko et al., 2020), microbial metabolites (Ji et al., 2020), minerals (Hengke et al., 2020) and vitamins (Praça et al., 2020), is useful to make the skin in an ideal situation. Whereas, some side-effects include the high cost, skin irritation, inflammatory reaction, and allergic limit their usage. Fortunately, some researchers found that bioactive peptides were highly safe and hypoallergenic (Bhandari et al., 2019) which have been widely used in cosmetics, medicine, functional foods, and other fields (Michalek et al., 2019; Zhang et al., 2020).

According to previous literatures, some bioactive peptides can regulate various biological processes in the skin epidermis and dermis to affect different functions of the skin by increasing the production of collagen, instead of the lost extracellular matrix, and improving skin wrinkles, fine lines, and tone (Malerich and Berson, 2014). At the present, a large number of literatures to discuss the studies and applications of anti-aging peptides in the prevention and treatment of skin aging.

With the growth of people's knowledge on cosmeceutical, the production of bioactive peptides with natural resources cannot meet the increasing demand of people. Therefore, some researchers use biotechnology to synthesize bioactive peptides (Bolhassani, 2019; Gorouhi and Maibach, 2015). On the one hand, it can increase the production efficiency of the bioactive peptide. On the other hand, researchers used a variety of methods to remedy the disadvantage of poor stability and low skin permeability, such as peptide structure modification, adjust the molecular weight of the peptide, or derivatization methods (Wu and Huang, 2018). In this work, we summarized the collagen peptides and the related synthetic peptides with the emphasis *in vitro*, *in vivo* and clinically to give a general understanding on improving skin health bioactive peptides.

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2. Skin aging

Skin, as the main barrier, is one of the main organs in our body. Similarly, skin, as a general term, plays an important role in balancing our temperature and dealing with environmental stimuli such as sunlight and pollutants (Tobin, 2006). As time goes by, our skin will through the process of aging naturally which will become dry, lack elasticity, and appear lines and wrinkles. The mechanism of skin aging is relatively complex. According to the causes of skin aging, it can be divided into internal aging and external aging. Compared with external aging, internal aging is due to the changes in cell metabolism, hormones, and metabolic processes, resulting in the decrease in the content of elastin, collagen, fibroblasts, hyaluronic acid, and other substances in the skin (Madiha et al., 2018). Thereby leading to skin wrinkles increased, dark skin, dry appearance, decreased elasticity and other obvious external aging phenomena. Lan et al. found that most external aging is mainly caused by long-term illumination without protection (Lan et al., 2019) and another study recovered that ultraviolet irradiation can increase free radicals and activate matrix metalloproteinases (MMPs) to degrade extracellular matrix, resulting in aging problems such as wrinkles (Quan and Fisher, 2015). Besides, other factors can also have certain effects on skin aging inside and outside, such as natural aging, heredity, malnutrition, pollution, diseases, and sub-health lifestyle, for example, smoking and sedentary (Tobin, 2017). External aging can be prevented and treated by changing skin structure and appearance. Compared with external aging, it is difficult for people to interfere with skin internal aging except using hormones (Aldag et al., 2016).

Based on these, bioactive peptides play an important role in the following aspects: (1) as enzyme inhibitors, inhibiting the enzyme activity directly or indirectly. For example, Pyun H-B et al. had shown that collagen peptide can reduce collagenase (matrix metalloproteinases: MMP-3 and MMP-13) and gelatinase activity (MMP-2 and MMP-9) (Pyun et al., 2012); (2) triggering signal cascade which can stimulate the proliferation of collagen, elastin, proteoglycans and glycosaminoglycans directly or indirectly (Proksch et al., 2014; Tałałaj et al., 2019); (3) inhibiting the transmission of neurotransmitters. Tetrapeptide-9 and tetrapeptide-11 can increase the chances of acetylcholine to bind with acetylcholine receptors on the surface of muscle cells by inhibiting the fusion of vesicles containing acetylcholine with the neuron membrane. It can enhance the muscle contraction and reduce the common signs of aging, such as wrinkles (Schagen et al., 2017); (4) as a carrier, delivering or stabilizing trace elements like manganese, contribute to wound healing (Ruiz et al., 2007). Therefore, bioactive peptides play an important role in the field of anti-aging.

Different sources of bioactive peptides have different biological activity, for example, the ACE inhibitory activity (IC50) of bovine collagen peptide (Val-Gly-Pro-Val) was significantly higher than synthetic peptide (leu-thr-Glu-Gln-Glu-ser-Gly-val-pro-val-met-Lys) in Table 1. Some researchers studied *in vitro*, *in vivo* and clinically to screen the biological activity of bioactive peptides which are from different sources. This review is based on the *vitro*, *in vivo* and clinical trials to explore the applications of collagen peptides and their synthetic peptides in cosmeceutical field and functional foods.

3. Anti-aging peptides with skin

The anti-aging peptides is the active peptides with anti-aging effect which can be divided into natural and synthetic anti-aging peptides. With the development of modern analysis technology, natural peptides and synthetic peptides were developed and utilized as a novel anti-aging produce. Most of the research centered on the treat and prevent skin external aging, researchers have found that collagen peptides play an important role in food supplements and cosmetics which can improve skin problems (Bolke et al., 2019; Kim et al., 2018). Synthetic peptides such as palmitoyl peptide and acetyl peptide can also improve skin health (Han et al., 2020; Han et al., 2021). Collagen peptides and synthetic peptides have been widely used in the production of anti-aging cosmetics and functional foods.

3.1. Collagen peptides

Collagen is one of the most widely distributed and abundant proteins in mammals. Generally used collagen types include I, II, III, IV, and other various collagen types. As a structural protein, it plays an important role in organizational structures, for example, the structural integrity and strength of tissues. Additionally, collagen protein can also support

Table 1
Different sources of anti-aging peptides with biological activities.

Type	Source	Sequences	Preparation	Antioxidant activity	Reference
Collagen peptides	Bullfrog skin	Leu-Glu- Glu- Leu-Glu-Glu- Glu-Leu-Glu-Gly-Cys-Glu	Six enzyme (Alcalase, neutrase, pepsin, papain, a-chymotrypsin and trypsin)	DPPH radical (IC50 = 16.1 μM); Hydroxyl radical (IC50 = 12.8 μM)	Qian et al. (2008)
	Bovine hair	Cys-Glu-Arg-Pro-Thr-Cys-Cys-Glu-His -Ser	Hydrolyzed at 90 ℃ for 24 h	Hydroxyl radical (IC50 = 35.40 μM)	Zeng et al. (2015)
	Duck processing by-products	Asp-Val-Cys-Gly-Arg-Asp-Val-Asn-Gly-Tyr	Nine proteases (Alcalase, Collaganase, Flavourzyme, Neutrase, Protamex, papain, pepsin, trypsin and -chymotrypsin)	Hydroxyl radical (IC50 = 59.56 μM)	S. J. Lee et al. (2010)
	Duck processing by-products	His-Thr-Val-Gln-Cys-Met-Phe-Gln		DPPH radical (IC50 = 20.28 μM); Hydroxyl radical (IC50 = 29.13 μM)	S. J. Lee et al. (2012)
	Oreochromis niloticus scales	Asp-Pro-Ala-Leu-Ala-Thr-Glu-Pro-Asp-ProMet-Pro-Phe	Alcalase, pronase E, trypsin and pepsin	DPPH radical (IC50 = 8.82 μM); Hydroxyl radical (IC50 = 7.56 μM)	Ngo et al. (2010)
	Salmon byproduct	Phe-Leu-Asn-Glu-Phe-Leu-His-Val	Serial digestion (Alcalase, Flavourzyme, Neutrase, pepsin, Protamex, and trypsin)	DPPH radical (IC50 = 486 μM)	Ahn et al. (2014)
Synthetic peptides	–	Trp-Tyr-Pro-Ala-Ala-Pro	Chemical synthesis	DPPH radical (IC50 = 18.5 μM); Hydroxyl radical (IC50 = 45.2 μM)	Seung Jae Lee et al. (2013)
	–	Leu-Thr-Glu-Gln-Glu-Ser-Gly-Val-Pro-Val-Met-Lys	Chemical synthesis	DPPH radical (IC50 = 144.1 μM); Hydroxyl radical (IC50 = 172.4 μM)	Tanzadehpanah et al. (2016)
		Thr-Glu-Gln-Glu-Ser-Gly-Val-Pro-Val-Met		DPPH radical (IC50 = 136.4 μM); Hydroxyl radical (IC50 = 140.3 μM)	
		Thr-Glu-Gln-Glu-Ser-Gly-Val-His-Val-Met		DPPH radical (IC50 = 134.6 μM); Hydroxyl radical (IC50 = 162.9 μM)	

connective tissues such as tendons, skin, teeth and stabilize cell structures in body tissues and strengthen them (Sliva et al., 2014; Gelse et al., 2003). Previous studies have shown that collagen can release bioactive peptides with a variety of physiological functions after enzymatic hydrolysis. These collagen hydrolysates and collagen-derived peptides obtained have positive effects in improving skin conditions (Kim et al., 2018; Song and Li, 2017).

Collagen can become water-soluble gelatin when heating. And the gelatin can prepare collagen peptides by enzymolysis. Pyun H-B et al. had shown that collagen peptide had different kinds of biological functions such as antioxidation, cell proliferation and chemotaxis. For example, it can inhibit dermal collagen decomposition by reducing collagenase (matrix metalloproteinases: MMP-3 and MMP-13) and gelatinase activity (MMP-2 and MMP-9), reducing skin moisture loss and wrinkling significantly, regulating skin hydration, increasing skin elasticity, and recovering collagen degradation and elastic fiber abnormalities caused by ultraviolet radiation (Pyun et al., 2012). Kang et al. used hairless mice exposed to ultraviolet radiation and some of them were fed collagen peptide of 1000 mg/kg for 9 weeks. They found that collagen peptide can increase the expression of hyaluronic acid synthase mRNA and skin moisturizing factor filaggrin, increase the content of hyaluronic acid in skin tissue, and down-regulate the expression of hyaluronidase (HYAL-1 and HYAL-2) mRNA (Kang et al., 2018). In other words, collagen peptide intake has a potential effect on avoiding skin moisture loss induced by ultraviolet (UVB) (Asserin et al., 2015). Animal tissue from livestock and poultry is the main way for people to obtain natural collagen and collagen peptides (Ahmed et al., 2020) (Fig. 1). In recent years, aquatic animals have the further in-depth developed and utilized due to their special advantages, such as low resistance and hypoallergenic.

Different sources of collagen peptides have different effects on anti-skin aging. Proksch et al. found that type I collagen-derived collagen peptide can stimulate the synthesis of procollagen I, elastin, and fibrin in the skin, increase the synthesis of dermal matrix and reduce the generation of eye wrinkles by ingesting collagen peptide derived from pig collagen I for 4–8 weeks (Proksch et al., 2014). Offengenden et al. indicated that the chicken-derived collagen peptide has significant effects on inflammatory changes, oxidative stress, collagen I synthesis, and cell proliferation through studying the effect of chicken-derived collagen peptide on human skin fibroblasts (Offengenden et al., 2018). Besides, it was also reported that oral administration of collagen peptide from bovine bone can improve skin relaxation by increasing skin collagen content and changing the ratio of type I and type III collagen, but it has no significant effect on skin moisturizing (Song et al., 2017). Additionally, the extraction of collagen peptides from aquatic animals has also been developed and used to improve skin problems. Some researchers had extracted collagen peptide whose sequence was YGDEY (Tyr-Gly-Asp-Glu-Tyr) from tilapia collagen hydrolysate. They found that it had various advantages such as increase the expression of antioxidation factor [superoxide dismutase (SOD) and glutathione (GSH)], maintain the balance between reduced glutathione and oxidized glutathione, enhance the generation of type I procollagen, reduce the level of reactive oxygen species (ROS) significantly in human keratinocytes (HaCaT), prevent DNA oxidative damage, and inhibit the expression of MMP-1 (collagenase) and MMP-9 (gelatinase), etc. In a word, YGDEY had the function of preventing ultraviolet (UVB)-induced damage to cells and inhibiting UVB-mediated photoaging of skin (Xiao et al., 2019). Additionally, Tkaczewska et al. found that Ala-Tyr dipeptide extracted from the carp skin hydrolysate had a high antioxidant capacity that can be used as an antioxidant. Compared with other antioxidant peptides, dipeptide has the advantages of small molecular weight, absorbed and can be utilized easily. It can be seen that dipeptide has certain advantages in the skin aging resistance. Thus, further in-depth research and development are necessary (Tkaczewska et al., 2019).

Different sources of collagen peptides have different effects on the skin. When the different sources of the collagen peptides among pig, cow, hen, and tilapia were compared for protecting against ultraviolet (UVA) induced fibroblast damage by acting them on human dermal fibroblasts (HDF), hen collagen peptides were found to be better than other collagen peptides (Wang et al., 2019).

Yaga Yuki et al. used stable isotope labeling and liquid phase mass spectrometry (LC-MS) technology to track oral collagen hydrolysate *in vivo*, indicated that collagen hydrolysate was hydrolyzed and absorbed in sequence in the gastrointestinal tract. Since collagen usually existed in a triple helix form in the Gly-Xaa-Yaa repeat form, the collagen hydrolysate absorbed into plasma was affected by the special structure. They usually existed in two forms: one is free amino acids such as proline (Pro), hydroxyproline (Hyp), X-Hyp dipeptide, X-Hyp-Gly tripeptide, and X-Hyp cyclic peptide, the other is various oligopeptides containing hydroxyproline, such as Pro-Hyp, Ala-Hyp, Gly-Pro, Hyp-Gly, Gly-Pro-Hyp and Ala-Hyp-Gly, Pro-Hyp-Gly (Taga et al., 2019). Shigemura et al. had studied that collagen hydrolysate has been taken continuously for 4 weeks. And they found a large number of protein hydrolysates produce dipeptides and tripeptides containing Hyp after digestion which was absorbed into the blood through peptide transporters on intestinal cells and distributed to various tissues through the blood circulation system. Since daily intake of collagen hydrolysate can promote the distribution and accumulation in tissues, it produced for the long-term corresponding biological activity on skin and joint cells (Shigemura et al., 2018). Similarly, Kamiyama et al. also proved that through oral administration of low molecular weight collagen hydrolysate to rats that dipeptides and tripeptides containing Hyp generated by protein hydrolysate after digestion reach various tissues through blood circulation. And compared with other tissues, skin was the final and most lasting site that they can even exist in the skin for up to 14 days (Watanabe-Kamiyama et al., 2009).

When the collagen hydrolysate and the collagen peptide show the anti-aging effect on the skin, the collagen peptide containing hydroxyproline has good stability under the action of the enzyme due to the property of hydroxyproline in the collagen hydrolysate after oral administration. It allows the collagen peptide to still exist in the form of the peptide after gastrointestinal digestion and can be better and stably

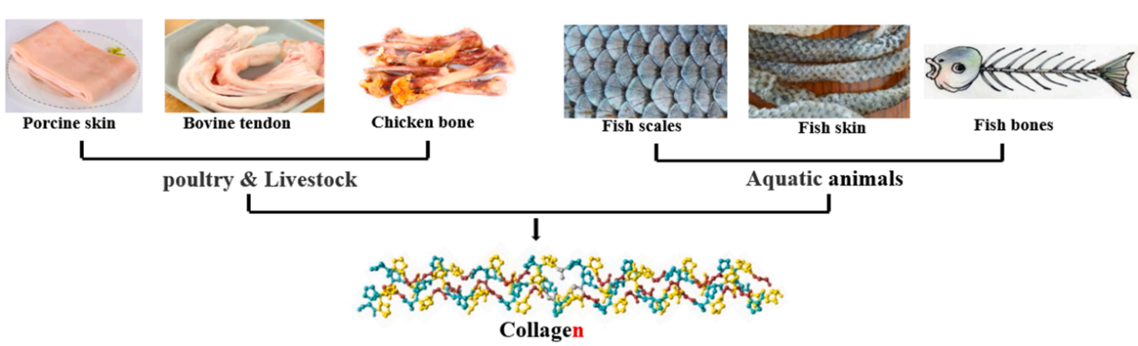

Fig. 1. Different sources of the collagen.

used in the skin anti-aging and other effects. Yazaki et al. found that the amount and type of collagen peptides in plasma and skin may be different due to the various source of ingested collagen peptides. And compared with other collagen peptides, the Pro-Hyp and Hyp-Gly sequences may be more important because they had certain biological activity on the skin (Yazaki et al., 2017). Shigemura et al. and Ohara et al. had proved that Pro-Hyp can stimulate the growth of mouse skin fibroblasts on collagen and also promote the production of hyaluronic acid by human skin fibroblasts (Ohara et al., 2010; Shigemura et al., 2009). Shigemura et al. found that Hyp-Gly can also increase the growth of mouse skin fibroblasts (Shigemura et al., 2011). And they also reported that it had a higher promotion effect on collagen gel growth of fibroblasts than Pro-Hyp in their other studies (Kusubata et al., 2015). Lee et al. prepared fish scale collagen peptide and studied its physiological function and they had proved that Gly-Pro dipeptide, as a representative low molecular weight peptide in fish scale collagen hydrolysate, was beneficial to skin health. Additionally, they had further research by feeding fish scale collagen hydrolysate, Gly-Pro, and Pro-Hyp separately to hairless mice whose dorsal skin exposed to ultraviolet. And they found that intake all of them could reduce the production of matrix metalloproteinase −1 and promote the synthesis of type I procollagen in human fibroblasts. What's more, the experimental results for 12 consecutive weeks showed that both Gly-Pro and Pro-Hyp could also improve ultraviolet-induced skin aging (Lee et al., 2019).

Only using natural resources to produce bioactive peptides cannot be enough to meet the growing needs of people. To solve the problem, people use biotechnology tools and processes to synthesize bioactive peptides. Compared with the traditional bioactive peptide, the synthesized bioactive peptide not only meets the needs of consumers, but the efficacy is higher.

3.2. Synthetic peptide

The polypeptide has good pharmacokinetic characteristics and can be absorbed, distributed, and metabolized in organisms. What's more, the polypeptide has strong biological activity. However, plenty of amide bonds which were as hydrogen bond donors and acceptor groups and too large molecular weight have led to the polypeptide cannot smoothly pass through the skin barrier, resulting in a low diffusion rate in the skin or its inability to diffuse into the skin inside which can make a certain negative effect on its usage (Christopher and Guy, 1992; Wu and Huang, 2018). Polypeptides have some characteristics; when applied topically, such as instability on the skin and low skin permeability which made challenges in the application of polypeptides for dermal, particularly delivery in the dermis. Along with the deepening of research, researchers used a great diversity of methods to resist peptidase degradation and improve low permeability, such as peptide structure modification, adjust the molecular weight of the peptide, or derivatization methods (Fig. 2). For example, the polypeptide can be modified by acetylation, glycosylation, and amidation at the N-terminal and the C-terminal. And after modification, the polypeptides have various advantages, such as increase the penetration of the polypeptide on the skin, the binding ability with special receptors, and the stability and solubility of bioactive peptide. Additionally, the polypeptide also can bind with palmitic acid to improve the low permeability when used topically. It thus prompted synthetic peptides can be utilized in local treatment (Bolhassani, 2019; Gorouhi and Maibach, 2010).

3.2.1. Palmitoyl peptide

Combination of fatty acids and peptides, as an effective method, has great potential in improving the stability and permeability of peptides (Benson and Namjoshi, 2008). As the highest abundance of fatty acid, palmitate can be used as a connecting element to the covalent modification of protein molecules. Foldvari et al. conducted a deep study on palmitoyl-derived α-interferon and indicated that it can increase by five times the penetration of natural protein into human skin due to the lipophilicity of palmitate residues (Foldvari et al., 1998). What' more, other studies indicated that palmitoyl binding polypeptide can also improve the penetration of the polypeptide in the skin. And compared with common polypeptide, the permeation rate can be increased by 100–1000 times (Dominik et al., 2015).

The pentapeptide with sequence Lys-Thr-Thr-Lys-Ser (KTTKS) in palmitoyl peptide is a carboxyl-terminal derived fragment of type I procollagen. Previous studies had shown that KTTKS can inhibit collagenase activity, stimulate the synthesis of elastin, fibronectin, glycosaminoglycan, and type I, type III, and type IV collagen, and it can significantly enhance extracellular matrix (ECM) and promote skin wound healing (Tałałaj et al., 2019). Taking advantage of its hydrophilicity and low skin permeability, Mortazavi et al. combined pentapeptide with 16-C fatty acid palmitate to form palmitoyl pentapeptide −4 (Pal-KTTKS-OH). And compared with KTTKS, the results showed that the permeability after modification increased, and the physical and

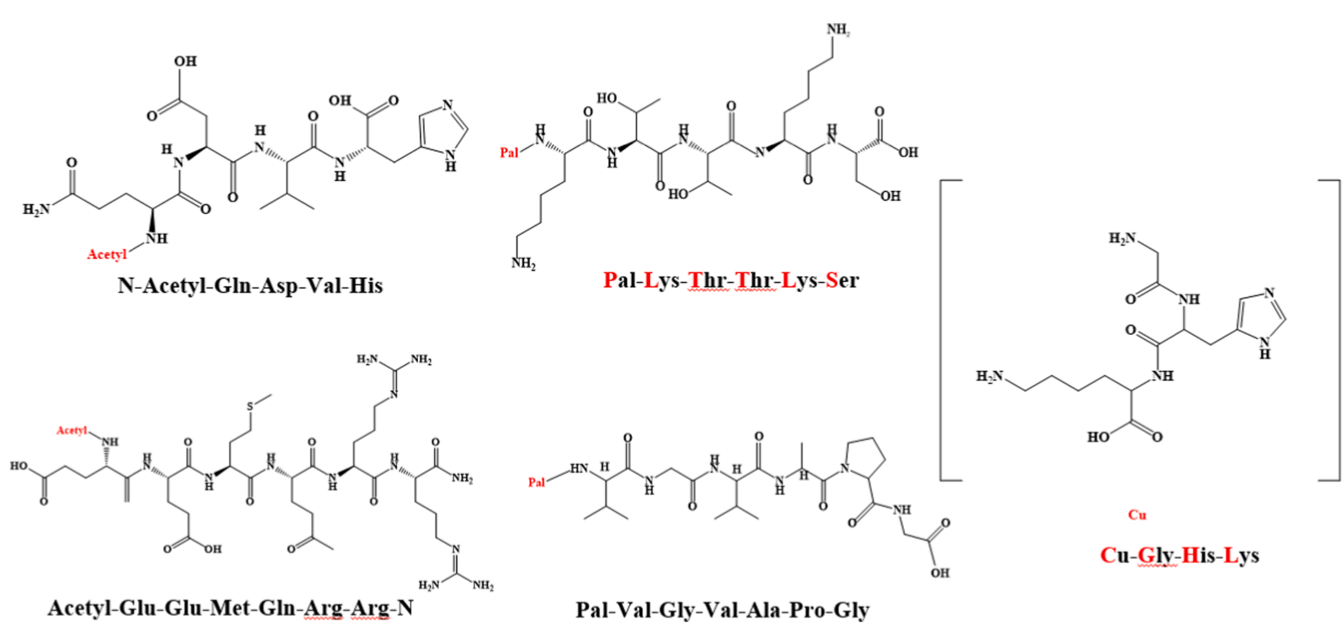

Fig. 2. Structure of the main synthetic anti-aging peptides.

chemical properties were also improved (Mortazavi et al., 2019). Additionally, Guttman et al. selected 49 women for a 4-month double-blind test using Pal-KTTKS twice a day. The results showed that Pal-KTTKS increased the density and thickness of elastin fibers, improved the regulation of type IV collagen at the dermal-epidermal junction, and significantly improved skin roughness, wrinkle volume, and wrinkle depth (Guttman, 2002). Additionally, Pal-KTTKS is one of the earliest polypeptides used in cosmetics.

In recent years, researchers have explored many polypeptides that are still active after binding with palmitic acids, such as Lys-Val-Lys (KVK), Lys-Met-Lys (KMK), Gly-His-Lys (GHK), Pal-Gly-Gln-Pro-Arg (GQPR), and Val-Gly-Val-Ala-Pro-Gly (VGVAPG). It has been proved in animal and clinical experiments that the combination of polypeptide and palmitic acid can reduce the generation of fine lines and wrinkles and resist the wrinkle effect. And both PAL-KVK (PALMITOYL TRI PEPTIDE-3/5) and Pal-GHK (Palmitoyl Tripeptide-1) can promote the formation of collagen protein. Besides, PAL-VGV APG (PALMITOIL HEXA PEPTIDE-12) can improve skin elasticity, tone, fatigue, and tightness by transforming skin cells, keratinocytes into cells, and fibroblasts and reducing the production of interleukin -6 (IL-6) (Schagen, 2017). Researches have developed many short and stable synthetic peptides that play an excellent role in extracellular matrix synthesis, pigmentation, innate immunity, and inflammation. In addition to palmitic acid, the modification of peptides by acetyl (Ac-) has great potential for using in anti-aging peptides.

3.2.2. Acetyl peptide

The majority of protein acetylation involves the binding of the acetyl group to lysine residue by acetyl donor, such as acetyl-CoA, through acetyl-converting enzyme (Allfrey et al., 1964; Narita et al., 2019). And the mostly acetylation of synthetic peptides occurs at the N-terminal of peptides. Overwhelming evidence indicates that acetylated peptides with anti-aging function have been developed and utilized. As shown in Table 2, as antioxidants, acetyl tetrapeptides (tetrapeptide-9, tetrapeptide-11) with the sequences of Gln-Asp-Val-His and Pro-Pro-Tyr-Leu have proven effective in stimulating the synthesis of type I collagen protein and basement membrane glycan, urging the growth of human keratinocytes and other advantages. Schagen et al. have found that tetrapeptide-9, tetrapeptide-11 can make the skin thicker and tighter through clinical research (Schagen et al., 2017). And compared with placebo, the effect of these peptides on the skin can be increased by 5%–10% (Gorouhi and Maibach, 2010). A similar trend was also reported by Wang Y et al., who investigated that sixty subjects were randomized to treatment with Glu-Glu-Met-Gln-Arg-Argacetyl hexapeptide (Argireline) and placebo, and the results showed that Argireline inhibited the docking of vesicles and affected the formation of wrinkles by interfering with the release of catecholamine which resulted in an effective rate up to 48.9% (Wang et al., 2013). What' more, Hajem et al. found that the acetyl tetrapeptide with the sequence of Ser-Asp-Lys-Pro could prevent skin aging and alopecia, and promote skin regeneration and hair growth (Hajem et al., 2013). Other studies also found that heptapeptide substance with sequence N-ACETYLASP-Glu-Glu-Thr-Gly-Glu-Phe-OH (ACETYL-DEET GEF-OH) can be applied in cosmetic formulations to protect skin cells from ultraviolet rays (Suter et al., 2016).

3.2.3. Copper/manganese tripeptide

Copper peptide is a small peptide with a molecular weight of 700 Daltons (da) chelated with Cu^{2+} and has good safety. In 1973, Picart et al. isolated copper tripeptide (Cu-GHK) and ~~he~~ found that the copper peptide with the sequence Gly-His-Lys can be used as human albumin active substance to synthesize protein which can make the liver tissue synthesizer in elderly population to be similar with the young people (Pickart, 2008). At present, the Cu-GHK complex is one of the most studied anti-aging peptides among copper peptides, which has the effects of promoting wound healing, and skin regeneration, reducing wrinkles, skin sagging, and pigmentation. What's more, it can stimulate the synthesis of collagen, elastin and glycosaminoglycan to improve the skin condition evidently (Pickart and Margolina, 2018). Leyden et al. and Finkley et al. discovered that skin elasticity, skin humidity, and wrinkles can be affected by adding Cu-GHK to the formula and applying it to women's skin. Thereby, it can significantly improve the appearance of damaged aging skin (Finkley et al., 2005; Leyden et al., 2002). Trace elements are necessary for the wound healing process, such as manganese (Mn). Interestingly, peptides can be used as transporters of trace elements. Ruiz et al. found that manganese tripeptide (GHK-Mn^{2+}) can also treat the light injury of the facial skin by adding it into facial serum preparations for 12 weeks (Ruiz et al., 2007).

Table 2
The anti-aging peptides derived from synthetic source.

Sequence	Abbreviation	Model	Function	Reference
N-Acetyl-Gln-Asp-Val-His	Acetyl tetrapeptide-9	Randomized clinical study	Stimulate the synthesis of type I collagen and basement membrane glycan	Rodrigues et al. (2009)
N-Acetyl-Pro-Pro-Tyr-Leu	tetrapeptide-11	Randomized clinical study	Stimulates the growth of human keratinocytes and the synthesis of transmembrane protein-polysaccharide	Rodrigues et al. (2009)
Acetyl-Glu-Glu-Met-Gln-Arg-Arg-NH2	Ac-EEMQRR-NH2 /Argireline	Placebo-controlled clinical trials	Inhibition of neurotransmitter release, anti-wrinkle, and moisturizing	Blanes-Mira et al. (2002)
N-Acetyl-Ser-Asp-Lys-Pro	Acetyl-SDKP	*Ex vivo* human skin-explant and hair follicle	Repair injured skin	Hajem et al. (2013)
N-Acetyl-Asp-Glu-Glu-Thr-Gly-Glu-Phe-oH	Acetyl-DEETGEF-OH	Double-blind clinical trials	Protect skin cells from UV damage	I. M. Michalek et al. (2019)
Pal-Lys-Thr-Thr-Lys-Ser	pal-KTTKS	Double-blind and placebo controlled clinical study	Anti-wrinkle, and moisturizing	Robinson et al. (2010)
Pal-Val-Gly-Val-Ala-Pro-Gly	pal-VGVAPG	murine embryonic skin	Anti-aging and moisturizing	Chang et al. (2008)
Mn-Gly-His-Lys	Mn-GHK	Normal human fibroblasts	Skin renewal	Ruiz et al. (2007)
Cu-Gly-His-Lys	Cu-GHK	Normal human fibroblasts	Skin renewal	Y., Wegrowski et al. (1992)

3.3. Application of polypeptides in cosmeceutical skin products

A polypeptide sequence is a chain consisting of more than 20 amino acids. In recent years, a variety of natural polypeptides and synthetic polypeptides which was obtained after modification by collagen have been confirmed to improve skin health. As time goes by, the understanding of anti-aging peptides has gradually deepening. As is shown in Table 3, these works demonstrated that so many anti-aging polypeptides can make the skin stromal cells regenerate, reduce UVB-induced skin pigmentation, decrease the fine lines and wrinkles, increase skin

Table 3
Bioactive peptide for resisting skin aging.

Name	Sequence	Abbreviation	Model	Functions	Reference
Carnosine	β-Ala-His	AH	Eleven-week-old male mice	Antioxidants, skin healing	Kim et al. (2019)
SYN-AKE	β-Ala-Pro-Dab-NHBn-2-Acetate	AP- Dab-NHBn-2-Acetate	Female subjects with moderate fine and thick wrinkles around the eyes	Reduce wrinkles	Trookman et al. (2009)
Trifluoroacetyl tripeptide −2	TFA-Val-Try-Val-OH	TFA-Vwv	Randomized clinical study	Affect skin wrinkles, firmness, elasticity, and sagging	LOING et al. (2012)
Citrulline tripeptide −10	Lys-α-Asp-Ile-Citrulline	KDI-Citrulline	Human skin tissue models	Increase skin elasticity	Michalek et al. (2019)
Tetrapeptide −21	Gly-Glu-Lys-Gly	GEKG	Randomized clinical study	Reduce skin roughness and increase skin elasticity	Jeong et al. (2020)
Tetrapeptide	Pro-Lys-Glu-Lys	PKEK	Human dermal fibroblasts and a 3D reconstituted human full skin model	Whitening and reducing UVB-induced skin pigmentation	Liang et al. (2019)
Pentapeptide −3	Gly-Pro-Arg-Pro-Ala	GPRPA	Placebo-controlled clinical study	Reduce wrinkles and skin roughness	Aguilar-Toalá et al. (2019)
Pentapeptide −18	Tyr-D-Ala-Gly-Phe-Leu	WAGFL	Randomized clinical study	Reduce fine lines and wrinkles, moisturize skin, improve skin firmness and skin color	Schagen (2017)
Hexapeptide −11	Phe-Val-Ala-Pro-Phe-Pro	FVAPFP	Placebo-controlled clinical study	Improve skin elasticity	Sklirou et al. (2015)

elasticity, and make the skin look smoother and firmer. Kim et al. found that carnosine can decrease the circulating levels of corticosterone and increase PI3K/Akt phosphorylation by establishing *in vivo* mouse aging model and injecting carnosine daily for 8 weeks, which indicating that carnosine had the potential to promote wound healing in aging skin (Kim et al., 2019). Trookman studied female subjects who applied SYN-AKE continuously for 12 weeks and found that SYN-AKE can increase the synthesis of collagen and significantly improve skin fine lines and wrinkles (Trookman, 2009). Liang et al. investigated the UVB-induced photoaging in human dermal fibroblasts and a 3D reconstituted human full skin model and found that tetrapeptide (Pro-Lys-Glu-Lys) could suppress the formation of matrix metalloproteinase-1 (MMP-1) and increase the expression level of collagen-1 and fibronectin-1 (Liang et al., 2019). Zhmak et al. researched the placebo-controlled clinical study and found that the pentapeptide -3(Gly-Pro-Arg-Pro-Ala) could increase the skin elasticity by enhancing the chances of acetylcholine to bind with acetylcholine receptors on the surface of muscle cells (Zhmak et al.,2015).

With the active peptide have been increasingly used in skin anti-aging since 2000, it has been found that a variety of sequence of

Table 4
Patents of synthetic peptides for anti-skin aging.

Sequence	Abbreviation	Model	Functions	Reference
X-Thr-Thr-Lys-Y	X-TTK-Y	Placebo-controlled clinical study	Stimulate healing, replenish water and improve wrinkles	Lintner (2003)
Lys-Leu-Asp-Ala-Pro-Thr	KLDAPT	Human fibroblasts and keratinocytes	Promoting skin cell adhesion to treat skin relaxation	Dal Farra and Domloge (2004)
$(Gly-Pro-Gln)_2$-NH2	$(GPQ)_2$-NH2	Human fibroblasts and keratinocytes	Promoting skin cell adhesion to treat skin relaxation	Dal Farra and Domloge (2007)
Leu-Lys-Lys-Thr-Glu-Thr	LKKTET	A subject with age spots	Increase skin elasticity and improve skin dullness due to aging	Goldstein (2004)
Lys-Val-Ile-Pro-Tyr-Val-Arg-Tyr-Leu	KVIPYVRYL	Human fibroblasts and keratinocytes	Alleviate or prevent skin aging	Smith (2009)
Val-Glu-Ile-Pro-Glu Tyr-Pro-Ile-Pro-Phe	VEIPE YPIPF	Placebo-controlled clinical study	Increase skin sensitivity	Lersch and Farwick (2010)
Pal-Lys-Thr	Pal-KT	Human fibroblasts	Skincare, improve skin condition	Lintner (2011)
Arg-Phe-Lys	RFK	Human fibroblasts	Reduce wrinkles	Ziegler et al. (2011)
Asp-Leu-Lys-Lys	DLKK	Human epidermis melanocytes	Limited the damage of UVB radiation to DNA of normal epidermal melanocytes	Domloge et al. (2016)
Pro-Arg-OH Pal-Pro-Arg-OH	PR-OH Pal-PR-OH	Human epidermis melanocytes and keratinocytes	Anti-aging peptide	Peschard and Mondon (2017)
Ala-Glu-Cys-Lys	AECK	Human dermal fibroblasts	Increase hyaluronic acid production of human dermal fibroblasts by 90–150%	Idkowiak-Baldys et al. (2017)
Glu-Leu-Lys-Leu-Ile-Phe-Leu-His-Arg-Leu-Lys-Arg-Leu-Arg-Lys-Arg-Leu-Lys-Arg-Lys His-Arg-Leu-Lys-Arg Leu-Lys-Arg-Leu-Arg Arg-Leu-Lys-Arg-Leu	ELKLIFLHRLKRLRKRLKRK HRLKR LKRLR RLKRL	Human dermal fibroblasts	Promote the growth of fibroblasts, promote the production of hyaluronic acid and collagen gel contraction	Nakagami et al. (2018)
Ile-Trp-Ser-Leu-Asp-Thr-Gln-Tyr-Gly-Arg-Gly-Asp	IWSLDTQYGRGD	Human dermal fibroblasts and melanoma cell	Inhibiting melanin production, tyrosinase activity, the expression of melanin related factors and the transfer of melanin bodies, and having a good skin whitening effect	Chung et al. (2018)
His-D-Trp-Ala-Trp-D-Phe-Lys-NH2	HWAWFK	Human dermal fibroblasts	Stimulating the expression of collagen I in human fibroblasts can reduce or delay cell senescence	Domloge et al. (2018)
β-L-Asp-L-Arg β-L-Asp-L-Lys	DR DK	Human keratinocytes	Stimulate basal keratinization and cell proliferation	Sallam et al. (2019)
NH2-Cys-Thr-Lys-Ile-Tyr-Asp-Pro-Val-Cys-COOH NH2-Cys-Pro-Arg-His-Phe-Asn-Pro-Val-Cys-COOH	CTKIYDPVC CPRHFNPVC	Human fibroblasts and keratinocytes	Inhibition of MMP2 activity, collagen degradation, and melanin transfer	Chung and Kim (2019)

bioactive peptides can be used in products. These bioactive peptides have extremely strong compatibility. They can not only be used in combination with a variety of antioxidants, such as ascorbic acid and its derivatives, catechins, curcumin, and ferulic acid derivatives, but chelate with trace elements such as copper and manganese (Idkowiak-Baldys et al., 2017; Nakagami et al., 2018). And the methods of the usage is easy. On the one hand, they can directly add into cosmeceutical skin products, such as milky lotions, facial essences, facial packs. On the other hand, they can be embedded by using a physiologically acceptable carrier to produce the pharmaceutical products (Nakagami et al., 2018). As shown in Table 4, a variety of bioactive peptides have been applied for many a patent due to their significant anti-aging properties. Lintner et al. randomly investigated 15 female subjects who treated with milky lotions contained tripeptide derivative (X-Thr-Thr-Lys-Y), compare with placebo, tripeptide derivative (X-Thr-Thr-Lys-Y) can induce the formation of partial collagen and glycosaminoglycan, protect and repair skin damage caused by ultraviolet radiation, and reduce skin surface wrinkles (Lintner et al., 2003). Goldstein et al. studied a subject with an age spot on the back of hand that used gel formulation containing Leu-Lys-Lys-Thr-Glu-Thr for consecutive 28 days and found that the age spot significantly fades within 7 days and noticeably decrease in size after 28 days. The results showed that the polypeptide with sequence Leu-Lys-Lys-Thr-Glu-Thr could reduce or reverse skin aging and enhance skin elasticity by inducing terminal deoxynucleotidyl transferase (a non-template-oriented DNA polymerase) (Goldstein et al., 2004). Lersch et al. selected 10 volunteers to conduct Placebo-controlled clinical study who should use the O/W cream containing oligopeptides (Val-Glu-Ile-Pro-Glu) or placebo twice a day with 10 days to the left volar forearm, respectively. The results showed that the synthetic peptide with the sequence of Val-Glu-Ile-Pro-Glu could be used as a neurotransmitter inhibitor to increase the neuronal perception of the skin and skin sensitivity and repair skin damaged cells timely (Lersch et al., 2010). Dal Farra et al. studied the human fibroblasts and keratinocytes incubated with synthetic peptide (Lys-Leu-Asp-Ala-Pro-Thr) and found that synthetic peptide (Lys-Leu-Asp-Ala-Pro-Thr) could increase adhesion between skin cells, provide curative and preventive treatment for ageing skin symptoms (of physiological or solar origin) and enhance skin appearance (Dal Farra and Domoge, 2007). Nakagami et al. found that synthetic peptide (Glu-Leu-Lys-Leu-Ile-Phe-Leu-His-Arg-Leu-Lys-Arg-Leu-Arg-Leu-Leu-Lys-Arg-Lys) achieved the excellent anti-aging effect by promoting human fibroblast growth, hyaluronic acid production, and contracting collagen gel contraction (Nakagami et al., 2018). What's more, Domlog et al. found that the synthetic peptide (His-D-TRP-Ala-TRP-D-Phe-Lys-NH2) could stimulate the production of matrix proteins, such as collagen, fibronectin, laminin, and decrease the compounds which modulated skin pigmentation to reduce or delay the appearance of cell senescence and signs of skin aging (Domlog et al., 2016). Nowadays, the amounts of peptides used in cosmeceutical products have dramatically increased which results in peptide sequences with cosmetic activity (such as anti-aging, anti-oxidation, whitening) have great commercial potential. As shown in Table 4, the patents for bioactive peptides for anti-skin aging, a variety of bioactive peptides are widely used in topical or cosmetic applications to improve the skin and the skin's nature.

4. Conclusions

Bioactive peptides have several advantages, including high activity, abundant sources, good absorption, and utilization *in vivo*. They are thus recognized by consumers due to their safety, high efficiency, and other characteristics. After topical application and oral administration, the natural and synthetic bioactive peptides can regenerate skin stromal cells, thereby reducing UVB-induced skin pigmentation, decreasing the fine lines and wrinkles, increasing skin elasticity, and promoting the skin to look smoother and firmer. In recent years, anti-aging peptides applied to skin local or integral has been extensively studied. Previous studies demonstrated that bioactive peptides have great potential in the cosmeceutical field. However, some of them are only *in vitro* and cell studies that have no clinical trials as guidance, and the protective mechanism has not been fully clarified. Previous reports have shown that polypeptides are beneficial in clinical treatment, but they still need to be further studied to obtain more details about the effectiveness of polypeptides and other mechanisms of action. At the same time, the large-scale screening, purification, and production of bioactive peptides still facing great challenges because amino acids and their order have certain effects on the activity of bioactive peptides. With the deepening of the bioactive of peptides and the gradual maturing production technology, the anti-aging function of bioactive peptides will have a great value in anti-aging.

Ethics statement

This review article did not involve any human subjects and animal experiments.

Finding

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CRediT authorship contribution statement

Xiaocao Zhao: Investigation, Writing - review & editing. **Xuejiao Zhang:** Investigation. **Dengyong Liu:** Conceptualization, Investigation, Project administration.

Declaration of Competing Interest

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

References

Aguilar-Toalá, J., Hernández-Mendoza, A., González-Córdova, A., Vallejo-Cordoba, B., & Liceaga, A. (2019). Potential role of natural bioactive peptides for development of cosmeceutical skin products. Peptides, 122, 170170. https://doi.org/ 10.1016/j.peptides.2019.170170.

Ahmed, M., Verma, A. K., & Patel, R. (2020). Collagen extraction and recent biological activities of collagen peptides derived from sea-food waste: A review. *Sustainable Chemistry and Pharmacy, 18*, Article 100315. https://doi.org/10.1016/j.scp.2020.100315.

Ahn, C. B., Kim, J. G., & Je, J. Y. (2014). Purification and antioxidant properties of octapeptide from salmon byproduct protein hydrolysate by gastrointestinal digestion. *Food Chemistry, 147*(mar.15), 78–83. https://doi.org/10.1016/j.foodchem.2013.09.136.

Aldag, C., Teixeira, D. N., & Leventhal, P. S. (2016). Skin rejuvenation using cosmetic products containing growth factors, cytokines, and matrikines: A review of the literature. *Clinical, Cosmetic and Investigational Dermatology, 9*, 411–419. https://doi.org/10.2147/CCID.S116158.

Allfrey, V., Faulkner, R., & Mirsky, A. (1964). Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. *Proceedings of the National Academy of Sciences of the United States of America, 51*(5), 786–794. https://doi.org/10.1073/pnas.51.5.786.

Asserin, J., Lati, E., Shioya, T., & Prawitt, J. (2015). The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: Evidence from an ex vivo model and randomized, placebo-controlled clinical trials. *Journal of Cosmetic Dermatology, 14*(4), 291–301. https://doi.org/10.1111/jocd.12174.

Benson, H. A., & Namjoshi, S. (2008). Proteins and peptides: Strategies for delivery to and across the skin. *Journal of Pharmaceutical Science, 97*(9), 3591–3610. https://doi.org/10.1002/jps.21277.

Bhandari, D., Rafiq, S., Gat, Y., Gat, P., Waghmare, R., & Kumar, V. (2019). A review on bioactive peptides: Physiological functions, bioavailability and safety. *International Journal of Peptide Research and Therapeutics, 26*(1), 139–150. https://doi.org/10.1007/s10989-019-09823-5.

Blanes-Mira, C., Clemente, J., Jodas, G., Gil, A., Fernández-Ballester, G., Ponsati, B., Gutierrez, L., Pérez-Payá, E., & Ferrer-Montiel, A. (2002). A synthetic hexapeptide (Argireline) with antiwrinkle activity. *International Journal of Cosmetic Science, 24*(5), 303–310. https://doi.org/10.1046/j.1467-2494.2002.00153.x.

Bolhassani, A. (2019). Improvements in chemical carriers of proteins and peptides. *Cell Biology International, 43*(4), 437–452. https://doi.org/10.1002/cbin.11108.

Bolke, L., Schlippe, G., Gerß, J., & Voss, W. (2019). A collagen supplement improves skin hydration, elasticity, roughness, and density: Results of a randomized, placebo-

controlled, blind study. *Nutrients, 11*(10), 2494. https://doi.org/10.3390/nu11102494.
Chang, C. H., Kawa, Y., Tsai, R. K., Shieh, J. H., Lee, J. W., Watabe, H., Kawakami, T., Soma, Y., Tajima, S., & Mizoguchi, M. (2008). Melanocyte precursors express elastin binding protein and elastin-derived peptide (VGVAPG) stimulates their melanogenesis and dendrite formation. *Journal of Dermatological Science, 51*(3), 158–170. https://doi.org/10.1016/j.jdermsci.2008.03.010.
Christopher, C., & Guy, Richard, H. (1992). (D) Routes of delivery: Case studies: (6) Transdermal delivery of peptides and proteins. Advanced Drug Delivery Reviews, 8 (2-3), 291-392. https://doi.org/10.1016/0169-409X(92)90006-C.
Chung, Y. J., & Kim, E. M. (2019). Peptide having activity to improve skin condition and use thereof. US20190040100, 2018-7-26.
Chung, Y. J., & Kim, E. M. (2019). Peptide having activity to improve skin condition and use thereof. US10487113, 2019-11-26.
Chung, Y. J., Kim, E. M., Eung-Ji, L., & Di, KIM. J. (2018). Peptide having skin whitening activity, and use thereof. EP3412275, 2018-12-12.
Dal Farra, C., & Domloge, N. (2007). Cosmetic or dermatological use of peptides for promoting adhesion between skin cells. US7211269, 2007-5-1.
Dal, Farra. C., & Domloge, N. (2004). Cosmetic or dermatological use of peptides for promoting adhesion between skin cells. US2004142873, 2004-7-22.
Dominik, I., Eileen, J., Marc, H., Remo, C., Eliane, W., & Hugo, Z. (2015). Activation of TGF-β: A gateway to skin rejuvenation. *Peptides, 10*(6), 6–11.
Domloge, N., Botto, J. -M., Serre, C., & Lebleu, A. (2016). Method to protect skin from ultraviolet radiation using novel peptides involved in the improvement of microparasol organization in keratinocytes. US9364414, 2016-6-14.
Domloge, N., Gondran, C., & Ludivine, M. (2018). Novel uses of the peptide of sequence his-d-trp-ala-trp-d-phe-lys-nh2 for reducing or delaying the appearance of cell senescence and signs of skin aging. EP3280387, 2019-7-3.
Domloge, N., Gondran, C., & Ludivine, M. (2018). Novel uses of the peptide of sequence his-d-trp-ala-trp-d-phe-lys-nh2 for reducing or delaying the appearance of cell senescence and signs of skin aging. US2018078483, 2018-03-22.
Finkley, M., Appa, Y., & Bhandarkar, S. (2005). Copper Peptide and Skin Cosmeceuticals and Active Cosmetics: Drugs vs. Cosmetics. Elsner, P., Maibach, H., Eds. Marcel Dekker: New York, USA.
Foldvari, M., Attah-Poku, S., Hu, J., Li, Q., Hughes, H., Lorne, A. B., & Kruger, S. (1998). Palmitoyl derivatives of interferon α: Potential for cutaneous delivery. *Journal of Pharmaceutical Science., 87*(10), 1203–1208. https://doi.org/10.1021/js980146k.
Gelse, K., Pöschl, E., & Aigner, T. (2003). Collagens—structure, function, and biosynthesis. *Advanced Drug Delivery Reviews, 55*(12), 1531–1546. https://doi.org/10.1016/j.addr.2003.08.002.
Goldstein, A. (2004). Inhibition or reversal of skin aging by actin-sequestering peptides. US2004067227, 2004-4-8.
Gorouhi, F., & Maibach, H. I. (2015). Topical peptides and proteins for aging skin. In M. Farage, K. Miller, & H. Maibach (Eds.), *Textbook of aging skin*. Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-642-27814-3_101-2.
Guttman, C. (2002). Studies demonstrate value of procollagen fragment Pal-KTTKS. *Dermatology Times, 23*(9).
Hajem, N., Chapelle, A., Bignon, J., Pinault, A., Liu, J. M., Salah-Mohellibi, N., Lati, E., & Wdzieczak-Bakala, J. (2013). The regulatory role of the tetrapeptide A c SDKP in skin and hair physiology and the prevention of ageing effects in these tissues–a potential cosmetic role. *International Journal of Cosmetic Science, 35*(3), 286–298. https://doi.org/10.1111/ics.12046.
Han, L. S., Himanshu, K., Bin, A. M. H., Xiyuan, Z., T. T. DH., Chi-Lui, H. P., & Lifeng, K. (2021). High resolution photopolymer for 3D printing of personalised microneedle for transdermal delivery of anti-wrinkle small peptide. Journal of Controlled Release, 329:907-918. https://doi.org/10.1016/J.JCONREL.2020.10.021.
Han, F., Luo, D., Qu, W., Chen, D., Hong, Y., Sheng, J., Yang, X., & Liu, W. (2020). Nanoliposomes codelivering bioactive peptides produce enhanced anti-aging effect in human skin. *Journal of Drug Delivery Science and Technology, 57*, Article 101693. https://doi.org/10.1016/j.jddst.2020.101693.
Hengke, G., Siyu, G., & Hongmei, L. (2020). Antioxidant activity and inhibition of ultraviolet radiation-induced skin damage of Selenium-rich peptide fraction from selenium-rich yeast protein hydrolysate. *Bioorganic Chemistry, 105*, Article 104431. https://doi.org/10.1016/J.BIOORG.2020.104431.
Idkowiak-Baldys, J., Lyga, J. W., & Santhanam, U. (2017). Peptides and Their Use in the Treatment of Skin. EP3236981, 2017-11-1.
Jeong, S., Yoon, S., Kim, S., Jung, J., Kor, M., Shin, K., Lim, C., Han, H. S., Lee, H., & Park, K.-Y. (2020). Anti-wrinkle benefits of peptides complex stimulating skin basement membrane proteins expression. *International Journal of Molecular Sciences, 21*(1), 73. https://doi.org/10.3390/ijms21010073.
Ji, K. H., Cheon, K. G., Gu, L. C., Sunhee, P., Garima, S., Ravi, V., Hyoeg, I. S., & Keun, K. H. (2020). Probiotics-derived metabolite ameliorates skin allergy by promoting differentiation of $FOXP^{3+}$ regulatory T cells. *Journal of Allergy and Clinical Immunology, 147*(4), 1517–1521. https://doi.org/10.1016/j.jaci.2020.11.040.
Kang, M. C., Yumnam, S., & Kim, S. Y. (2018). Oral intake of collagen peptide attenuates ultraviolet B irradiation-induced skin dehydration *in vivo* by regulating hyaluronic acid synthesis. *International Journal of Molecular Science, 19*(11), 3551. https://doi.org/10.3390/ijms19113551.
Karami, Z., & Akbari-adergani, B. (2019). Bioactive food derived peptides: A review on correlation between structure of bioactive peptides and their functional properties. *Journal of Food Science and Technology-MYS, 56*(2), 535–547. https://doi.org/10.1007/s13197-018-3549-4.
Kim, D.-U., Chung, H.-C., Choi, J., Sakai, Y., & Lee, B.-Y. (2018). Oral intake of low-molecular-weight collagen peptide improves hydration, elasticity, and wrinkling in human skin: A randomized, double-blind, placebo-controlled study. *Nutrients, 10*(7), 826. https://doi.org/10.3390/nu10070826.
Kim, Y., Kim, E., & Kim, Y. (2019). l-histidine and l-carnosine accelerate wound healing via regulation of corticosterone and PI3K/Akt phosphorylation in d-galactose-induced aging models *in vitro* and *in vivo*. *Journal of Functional Foods, 58*, 227–237. https://doi.org/10.1016/j.jff.2019.04.060.
Ko, H. J., Kim, J. H., Lee, G. S., & Shin, T. (2020). Sulforaphane controls the release of paracrine factors by keratinocytes and thus mitigates particulate matter-induced premature skin aging by suppressing melanogenesis and maintaining collagen homeostasis. *Phytomedicine, 77*, Article 153276. https://doi.org/10.1016/j.phymed.2020.153276.
Kusubata, M., Koyama, Y-i, Tometsuka, C., Shigemura, Y., & Sato, K. (2015). Detection of endogenous and food-derived collagen dipeptide prolylhydroxyproline (Pro-Hyp) in allergic contact dermatitis-affected mouse ear. *Bioscience, Biotechnology, and Biochemistry, 79*(8), 1356–1361. https://doi.org/10.1080/09168451.2015.1027653.
Lan, C.-C. E., Hung, Y.-T., Fang, A.-H., & Ching-Shuang, W. (2019). Effects of irradiance on UVA-induced skin aging. *Journal of dermatological Science, 94*(1), 220–228. https://doi.org/10.1016/j.jdermsci.2019.03.005.
Lee, S. J., Cheong, S. H., Kim, Y. S., Hwang, J. W., Kwon, H. J., Kang, S. H., Moon, S. H., Jeon, B. T., & Park, P. J. (2013). Antioxidant activity of a novel synthetic hexa-peptide derived from an enzymatic hydrolysate of duck skin by-products. *Food and Chemical Toxicology, 62*, 276–280. https://doi.org/10.1016/j.fct.2013.08.054.
Lee, H.-J., Jang, H.-L., Ahn, D.-K., Kim, H.-J., Jeon, H. Y., Seo, D. B., Lee, J.-H., Choi, J. K., & Kang, S.-S. (2019). Orally administered collagen peptide protects against UVB-induced skin aging through the absorption of dipeptide forms, Gly-Pro and Pro-Hyp. *Bioscience, Biotechnology, and Biochemistry, 83*(6), 1146–1156. https://doi.org/10.1080/09168451.2019.1580559.
Lee, S. J., Kim, Y. S., Hwang, J. W., Kim, E. K., Moon, S. H., Jeon, B. T., Jeon, Y. J., Kim, J. M., & Park, P. J. (2012). Purification and characterization of a novel antioxidative peptide from duck skin by-products that protects liver against oxidative damage. *Food Research International, 49*(1), 285–295. https://doi.org/10.1016/j.foodres.2012.08.017.
Lee, S. J., Kim, E. K., Hwang, J. W., Oh, H. J., Cheong, S. H., Moon, S. H., Jeon, B. T., Sang, M. L., & Park, P. J. (2010). Purification and characterisation of an antioxidative peptide from enzymatic hydrolysates of duck processing by-products. *Food Chemistry, 123*(2), 216–220. https://doi.org/10.1016/j.foodchem.2010.04.001.
Lersch, P., & Farwick, M. (2010). Dermatological compositions including oligopeptides for increasing skin sensitivity and neuronal perception. US7858580, 2010-12-28.
Leyden, J., Stevens, T., Finkey, M., Barkovic, S. (2002). Skin care benefits of copper peptide containing facial cream. In: American Academy of Dermatology 60th Annual Meeting, 2002. American Academy of Dermatology, 29. https://doi.org/10.1007/978-3-540-71097-4_7.
Liang, Y., Wu, M., & Chen, Y. (2019). Selected medicinal herbs and functional peptides for protection against photoaging of the skin. *Journal of Cosmetics, Dermatological Sciences and Applications, 9*(1), 1–18. https://doi.org/10.4236/jcdsa.2019.91001.
Lintner, K. (2003). Cosmetic or dermopharmaceutical use of peptides for healing, hydrating and improving skin appearance during natural or induced ageing (heliodermia, pollution). US6620419, 2003-9-16.
Lintner, K. (2011). Lys-Thr dipeptides and their use. EP1885741, 2011-9-14.
Loing, E., Suere, T., & Lamarque, E. (2012). Trifluoroacetyl-tripeptide-2 to target senescence for anti-aging benefits. *Cosmetics and Toiletries, 127*(4), 274–280.
Madiha, F., Mehran, R., Alia, N., & Awan, S. J. (2018). A systematic review of aging and its causes. *International Journal of Development Research, 8*(11), 23904–23908. http://www.journalijdr.com.
Malerich, S., & Berson, D. (2014). Next generation cosmeceuticals: The latest in peptides, growth factors, cytokines, and stem cells. *Dermatologic Clinics, 32*(1), 13–21. https://doi.org/10.1016/J.Det.2013.09.003.
Michalek, I. M., Lelen-Kaminska, K., & Caetano, dos. Santos. F. L. (2019). Peptides stimulating synthesis of extracellular matrix used in anti-ageing cosmetics: Are they clinically tested? A systematic review of the literature. Australasian Journal of Dermatology, 60(4), 267-271. https://doi.org/10.1111/ajd.13036.
Mortazavi, S. M., Kobarfard, F., Maibach, H. I., & Moghimi, H. R. (2019). Effect of palmitic acid conjugation on physicochemical properties of peptide KTTKS: A preformulation study. *Journal of Cosmetic Science, 70*(6), 299–312.
Nakagami, H., Morishita, R., Tomioka, H., & Tenma, A. (2018). Peptide with anti-aging effect and use thereof. US2018110713, 2018-4-26.
Narita, T., Weinert, B. T., & Choudhary, C. (2019). Functions and mechanisms of non-histone protein acetylation. *Nature Reviews Molecular Cell Biology, 20*(3), 156–174. https://doi.org/10.1038/s41580-018-0081-3.
Ngo, D. H., Qian, Z. J., Ryu, B. M., Park, J. W., & Kim, S. K. (2010). *In* vitro antioxidant activity of a peptide isolated from Nile tilapia (Oreochromis niloticus) scale gelatin in free radical-mediated oxidative systems. *Journal of Functional Foods, 2*(2), 107–117. https://doi.org/10.1016/j.jff.2010.02.001.
Offengenden, M., Chakrabarti, S., & Wu, J. (2018). Chicken collagen hydrolysates differentially mediate anti-inflammatory activity and type I collagen synthesis on human dermal fibroblasts. *Food Science and Human Wellness, 7*(2), 138–147. https://doi.org/10.1016/j.fshw.2018.02.002.
Ogori, A., Girgih, A., Abu, J., & Eke, M. (2019). Food derived bioactive peptides for health enhancement and management of some chronic diseases. *Asian Food Science Journal, 1–11*. https://doi.org/10.9734/afsj/2019/v8i130011.
Ohara, H., Ichikawa, S., Matsumoto, H., Akiyama, M., Fujimoto, N., Kobayashi, T., & Tajima, S. (2010). Collagen-derived dipeptide, proline-hydroxyproline, stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts. *Journal of Dermatology, 37*(4), 330–338. https://doi.org/10.1111/j.1346-8138.2010.00827.x.
Peschard, O., & Mondon, P. (2017). Pro-pigmenting peptides. US2017071844, 2017-3-16.

Pickart, L. (2008). The human tri-peptide GHK and tissue remodeling. *Journal of Biomaterials Science Polymer Edition, 19*(8), 969–988. https://doi.org/10.1163/156856208784909435.

Pickart, L., & Margolina, A. (2018). Skin regenerative and anti-cancer actions of copper peptides. *Cosmetics, 5*(2), 29. https://doi.org/10.3390/cosmetics5020029.

Praça, F. G., Viegas, J. S. R., Peh, H. Y., Garbin, T. N., Medina, W. S. G., & Bentley, M. V. L. B. (2020). Microemulsion co-delivering vitamin A and vitamin E as a new platform for topical treatment of acute skin inflammation. *Materials Science and Engineering. C-Materials for Biological Applications, 110*, Article 110639. https://doi.org/10.1016/j.msec.2020.110639.

Proksch, E., Schunck, M., Zague, V., Segger, D., Degwert, J., & Oesser, S. (2014). Oral intake of specific bioactive collagen peptides reduces skin wrinkles and increases dermal matrix synthesis. *Skin Pharmacology and Physiology, 27*(3), 113–119. https://doi.org/10.1159/000355523.

Pyun, H.-B., Kim, M., Park, J., Sakai, Y., Numata, N., Shin, J.-Y., Shin, H.-J., Kim, D.-U., & Hwang, J.-K. (2012). Effects of collagen tripeptide supplement on photoaging and epidermal skin barrier in UVB-exposed hairless mice. *Preventive Nutrition and Food Science, 17*(4), 245–253. https://doi.org/10.3746/pnf.2012.17.4.245.

Qian, Z. J., Jung, W. K., & Kim, S. K. (2008). Free radical scavenging activity of a novel antioxidative peptide purified from hydrolysate of bullfrog skin, Rana catesbeiana Shaw. *Bioresource Technology, 99*(6), 1690–1698. https://doi.org/10.1016/j.biortech.2007.04.005.

Quan, T., & Fisher, G. J. (2015). Role of age-associated alterations of the dermal extracellular matrix microenvironment in human skin aging: A mini-review. *Gerontology, 61*(5), 427–434. https://doi.org/10.1159/000371708.

Robinson, L. R., Fitzgerald, N. C., Doughty, D. G., Dawes, N. C., Berge, C. A., & Bissett, D. L. (2010). Topical palmitoyl pentapeptide provides improvement in photoaged human facial skin. *International Journal of Cosmetic Science, 27*(3), 155–160. https://doi.org/10.1111/j.1467-2494.2005.00261.x.

Rodrigues, A. L. B., I.; Clarius, & T. Pauly, G. (2009). Counter acting Ageing Phenomena by New Pure Tetrapeptides with Targeted Efficacy. Journal of Applied Cosmetology, 27, 63-71.

Ruiz, M., Clares, B., Morales, M., Cazalla, S., & Gallardo, V. (2007). Preparation and stability of cosmetic formulations with an anti-aging peptide. *Journal of Cosmetic Science, 58*(2), 157–171. https://doi.org/10.1111/j.1468-2494.2007.00401_4.x.

Sallam, A., Krehenbrink, M., & Kalkandzhiev, D. (2019). Aspartyl-dipeptides for skin care and cosmetic use. EP3439626,2019-2-13.

Sallam, A., Krehenbrink, M., & Kalkandzhiev, D. (2019). Aspartyl-dipeptides for skin care and cosmetic use. US2019117548, 2019-4-25.

Schagen, S. K. (2017). Topical peptide treatments with effective anti-aging results. *Cosmetics, 4*(2), 16. https://doi.org/10.3390/cosmetics4020016.

Shigemura, Y., Akaba, S., Kawashima, E., Park, E. Y., Nakamura, Y., & Sato, K. (2011). Identification of a novel food-derived collagen peptide, hydroxyprolyl-glycine, in human peripheral blood by pre-column derivatisation with phenyl isothiocyanate. *Food Chemistry, 129*(3), 1019–1024. https://doi.org/10.1016/j.foodchem.2011.05.066.

Shigemura, Y., Iwai, K., Morimatsu, F., Iwamoto, T., Mori, T., Oda, C., Taira, T., Park, E. Y., Nakamura, Y., & Sato, K. (2009). Effect of prolyl-hydroxyproline (Pro-Hyp), a food-derived collagen peptide in human blood, on growth of fibroblasts from mouse skin. *Journal of Agricultural and Food Chemistry, 57*(2), 444–449. https://doi.org/10.1021/jf802785h.

Shigemura, Y., Suzuki, A., Kurokawa, M., Sato, Y., & Sato, K. (2018). Changes in composition and content of food-derived peptide in human blood after daily ingestion of collagen hydrolysate for 4 weeks. *Journal of the Science of Food and Agriculture, 98*(5), 1944–1950. https://doi.org/10.1002/jsfa.8677.

Sklirou, A. D., Ralli, M., Dominguez, M., Papassideri, I., Skaltsounis, A.-L., & Trougakos, I. P. (2015). Hexapeptide-11 is a novel modulator of the proteostasis network in human diploid fibroblasts. *Redox Biology, 5*, 205–215. https://doi.org/10.1016/j.redox.2015.04.010.

Smith, J. A. (2009). Casein peptides for alleviating or preventing aging of skin. US7579315, 2009-8-25.

Song, H., & Li, B. (2017). Beneficial effects of collagen hydrolysate: a review on recent developments. Journal of Scientific and Technical Research, 1(2), 1-4. https://doi.org/10.26717/BJSTR.2017.01.000217.

Song, H., Zhang, S., Zhang, L., & Li, B. (2017). Effect of orally administered collagen peptides from bovine bone on skin aging in chronologically aged mice. *Nutrients., 9*(11), 1209. https://doi.org/10.3390/nu9111209.

Suter, F., Schmid, D., Wandrey, F., & Zülli, F. (2016). Heptapeptide-loaded solid lipid nanoparticles for cosmetic anti-aging applications. *European Journal of Pharmaceutics and Biopharmaceutics, 108*, 304–309. https://doi.org/10.1016/j.ejpb.2016.06.014.

Taga, Y., Iwasaki, Y., Shigemura, Y., & Mizuno, K. (2019). Improved *in vivo* tracking of orally administered collagen hydrolysate using stable isotope labeling and LC–MS techniques. *Journal of Agricutural and Food Chemistry, 67*(16), 4671–4678. https://doi.org/10.1021/acs.jafc.9b00571.

Tałałaj, U., Uścinowicz, P., Bruzgo, I., Surażyński, A., Zaręba, I., & Markowska, A. (2019). The effects of a novel series of KTTKS analogues on cytotoxicity and proteolytic activity. *Molecules, 24*(20), 3698. https://doi.org/10.3390/molecules24203698.

Tanzadehpanah, H., Asoodeh, A., Mahaki, H., Mostajabodave, Z., Chamani, J., Mojallal-Tabatabaei, Z., … Moradi, M.-R. (2016). Bioactive and ACE binding properties of three synthetic peptides assessed by various spectroscopy techniques. *Process Biochemistry, 51*(12), 2067–2075. https://doi.org/10.1016/j.procbio.2016.09.017.

Tkaczewska, J., Bukowski, M., & Mak, P. (2019). Identification of antioxidant peptides in enzymatic hydrolysates of carp (Cyprinus Carpio) skin gelatin. *Molecules, 24*(1), 97. https://doi.org/10.3390/molecules24010097.

Tobin, D. J. (2006). Biochemistry of human skin—our brain on the outside. *Chemical Society Reviews, 35*(1), 52–67. https://doi.org/10.1039/B505793K.

Tobin, D. J. (2017). Introduction to skin aging. *Journal of Tissue Viability, 26*(1), 37–46. https://doi.org/10.1016/j.jtv.2016.03.002.

Trookman, N. S., Rizer, R. L., Ford, R., Ho, E., & Gotz, V. (2009). Immediate and long-term clinical benefits of a topical treatment for facial lines and wrinkles. *The Journal of Clinical and Aesthetic Dermatology, 2*(3), 38. https://doi.org/10.1016/j.jaad.2008.11.364.

Wang, X., Hong, H., & Wu, J. (2019). Hen collagen hydrolysate alleviates UVA-induced damage in human dermal fibroblasts. *Journal of Functional Foods, 63*, Article 103574. https://doi.org/10.1016/j.jff.2019.103574.

Wang, Y., Wang, M., Xiao, S., Pan, P., Li, P., & Huo, J. (2013). The anti-wrinkle efficacy of argireline, a synthetic hexapeptide, in Chinese subjects. *American Journal of Clinical Dermatology, 14*(2), 147–153. https://doi.org/10.1007/s40257-013-0009-9.

Watanabe-Kamiyama, M., Shimizu, M., Kamiyama, S., Taguchi, Y., Sone, H., Morimatsu, F., … Komai, M. (2009). Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats. *Journal of Agricultural and Food Chemistry, 58*(2), 835–841. https://doi.org/10.1021/jf9031487.

Wu, H., & Huang, J. (2018). Optimization of protein and peptide drugs based on the mechanisms of kidney clearance. *Protein and Peptide Letters, 25*(6), 514–521. https://doi.org/10.2174/0929866525666180530122835.

Xiao, Z., Liang, P., Chen, J., Chen, M. F., Gong, F., Li, C., Zhou, C., Hong, P., Yang, P., & Qian, Z. J. (2019). A peptide YGDEY from tilapia gelatin hydrolysates inhibits UVB-mediated skin photoaging by regulating MMP-1 and MMP-9 expression in HaCaT cells. *Photochemistry and Photobiology, 95*(6), 1424–1432. https://doi.org/10.1111/php.13135.

Y., Wegrowski, F., X., Maquart, and, J., P., & Borel. (1992). Stimulation of sulfated glycosaminoglycan synthesis by the tripeptide-copper complex Glycyl-L-histidyl-L-lysine-Cu2+. Life Sciences, 51(13), 1049. https://doi.org/10.1016/0024-3205(92)90504-I.

Yazaki, M., Ito, Y., Yamada, M., Goulas, S., Teramoto, S., Nakaya, M.-a., Ohno, S., & Yamaguchi, K. (2017). Oral ingestion of collagen hydrolysate leads to the transportation of highly concentrated Gly-Pro-Hyp and its hydrolyzed form of Pro-Hyp into the bloodstream and skin. *Journal of Agriculture and Food Chemistry, 65*(11), 2315–2322. https://doi.org/10.1021/acs.jafc.6b05679.

Zeng, W. C., Zhang, W. H., He, Q., & Shi, B. (2015). Purification and characterization of a novel antioxidant peptide from bovine hair hydrolysates. *Process Biochemistry, 50*(6), 948–954. https://doi.org/10.1016/j.procbio.2015.03.007.

Zhang, Z., Zhu, H., Zheng, Y., Zhang, L., Wang, X., Luo, Z., Tang, J., Lin, L., Du, Z., & Dong, C. (2020). The effects and mechanism of collagen peptide and elastin peptide on skin aging induced by D-galactose combined with ultraviolet radiation. *Journal of Photochemistry and Photobiology, B: Biology, 210*, Article 111964. https://doi.org/10.1016/j.jphotobiol.2020.111964.

Zhmak, M. N., Utkin, Y. N., Andreeva, T. V., Kudryavtsev, D. S., Kryudova, E. V., Tsetlin, V. I., Kasheverov, I. E. e., Starkov, V. G. e., & Shelukhina, I. V. e. Peptide inhibitors of nicotinic acetylcholine receptor. US2015361137,2015-12-17.

Ziegler, H., Heidl, M., & Imfeld, D. (2011). Tripeptides and derivatives thereof for cosmetic application in order to improve skin structure. US2011142895, 2011-6-16.