Topical peptides as cosmeceuticals

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**ABSTRACT**

Peptides are known to have diverse biological roles, most prominently as signaling/regulatory molecules in a broad variety of physiological processes including defense, immunity, stress, growth, homeostasis and reproduction. These aspects have been used in the field of dermatology and cosmetology to produce short, stable and synthetic peptides for extracellular matrix synthesis, pigmentation, innate immunity and inflammation. The evolution of peptides over the century, which started with the discovery of penicillin, has now extended to their usage as cosmeceuticals in recent years. Cosmeceutical peptides may act as signal modulators of the extracellular matrix component, as structural peptides, carrier peptides and neurotransmitter function modulators. Transdermal delivery of peptides can be made more effective by penetration enhancers, chemical modification or encapsulation of peptides. The advantages of using peptides as cosmeceuticals include their involvement in many physiological functions of the skin, their selectivity, their lack of immunogenicity and absence of premarket regulatory requirements for their use. However, there are disadvantages: clinical evidence for efficacy is often weak, absorption may be poor due to low lipophilicity, high molecular weight and binding to other ingredients, and prices can be quite high.

Key words: Cosmeceuticals, dermatotherapeutics, topical peptides

**INTRODUCTION**

A peptide is a group of amino acids linked by peptide bonds. In terms of chemical complexity, peptides fill a position between typical small molecule chemicals and the larger proteins.\(^{[1,2]}\) Naturally occurring peptides are known to have diverse biological roles, most prominently as signaling/regulatory molecules in a broad variety of physiological processes including defense, immunity, stress, growth, homeostasis and reproduction.\(^{[1]}\) Recently, the dermatology and cosmeceutical industry has developed short, stable and synthetic peptides that have a role in extracellular matrix synthesis, pigmentation, innate immunity and inflammation.\(^{[3]}\)

The peptides were initially considered ineligible for drug development because of the presence of roughly 600 proteases which degrade these peptides within the body.\(^{[4]}\) However, recent technological advances have again sparked major interest in their usage, both in diagnostics as well as therapeutics.\(^{[1]}\)

**EVOLUTION OF PEPTIDES**

Although peptides were among the initial therapeutic discoveries around a century ago (opioids, cyclic peptide penicillin and polypeptide insulin), the role of oligopeptides (<20 amino acids) became clearer only around half a century later when du Vigneau and Tuppy discovered and characterized the chemical structure of the first peptide hormone, the octapeptide oxytocin and later, other biological mediators such as angiotensin, vasopressin and bradykinin.\(^{[1,2]}\)
Later, small molecules rapidly took preference in the drug development industry primarily due to their ease of production, simplicity of administration and superior pharmacodynamic properties.[1]

Oligopeptides have been used in medicine for some time but their role in affecting biological activity within the skin has only recently been explored with etanercept and cyclosporine being the two most commonly used peptides in dermatology.[2,5]

The use of peptides has now been extended as cosmeceuticals, a concept introduced by Dr. Kligman for agents distributed across a broad spectrum, lying somewhere between pure cosmetics and drugs.[6] Cosmeceuticals are products that deliver a biologic activity in support of cosmetic claims.[3] The market for peptides is estimated to reach US $25 billion or 10% of the pharmaceutical market and is growing at a rate faster than that of small molecules.[10] In terms of revenue generated, by year 2016, the global cosmeceutical market was estimated to reach $31.84 billion.[8]

A classification of peptides is given in Table 1[9] and a list of commonly used peptides is given in Table 2.[2,3,9]

### USE OF PEPTIDES

**Signal modulation of extracellular matrix proteins**

Natural aging of skin results in decreased production and increased degradation of extracellular matrix proteins such as collagen, fibronectin, elastin and laminin.[2] The extracellular matrix, in addition to providing structural support, also influences cellular behavior such as differentiation and proliferation. These functions are mediated through small peptides (matrikines) derived from proteolytic degradation of extracellular matrix protein. These matrikines act as signal proteins between matrix component and cell wall receptors.[3]

**Signal peptides modulating collagen**

Various peptides affect the aging process by modulating collagen homeostasis. Pentapeptide-3 (Lys-Thr-Thr-Lys-Ser, KTTKS) was one of the first oligopeptides to be developed as a cosmetic agent.[2] It is a subfragment of the carboxyl-terminal propeptide of type I collagen.[10] This peptide fragment dramatically augmented extracellular matrix production in the fibroblasts. It also stimulates type I and type III collagen and fibronectin production in a dose- and time-dependent manner with no effect on total protein synthesis or the ratio of secreted proteins to cell-associated proteins.[3,10,11] When such peptides are used topically, their instability on or in the skin and poor permeability across the skin are challenges for successful dermal delivery. To overcome this handicap, the peptide was conjugated with a fatty acid, i.e., palmitic acid (pal-KTTS) to increase stability and penetration into the skin.[12-14] A study in 180 women by Osborne et al. showed that pal-KTTKS significantly decreased the bumpy texture and fine lines as compared to controls.[15]

Tripeptide-1 (glycyl-l-histidyl-l-lysine) can be also conjugated with palmitic acid and form pal-tripeptide-1. In vitro and in vivo studies proved that this combination stimulates the synthesis of collagen and glycosaminoglycans.[9]

Matrix metalloproteinases form an important family of metal-dependent endopeptidases that represent the major class of enzymes responsible for degradation of components of the extracellular matrix. Upregulation of matrix metalloproteinases occurs in aging. Enzymatic studies demonstrated that tripeptide-2 inhibits active matrix metalloproteinases and minimizes the excessive dermal matrix breakdown seen in photoaging and chronological aging.[16] Trifluorotripeptide-2 also decreases the production of progerin which along with dysfunctioning telomeres can induce senescence. Therefore, this peptide regulates biological mechanisms involved in the aging process.[17]

Palmitoyl tripeptide-5 (palmitoyl-lysyl-valyl-lysine) is a synthetic signal peptide which mimics thrombospondin which causes the sequence Arg-PheLys to bind to the inactive form of transforming growth factor-β inducing a release of active transforming growth factor-β.[18] In a controlled trial, 60 healthy volunteers received 2.5% palmitoyl tripeptide-5 versus 10% palmitoyl pentapeptide-3 cream versus placebo cream twice daily for 84 days. Palmitoyl tripeptide-5 significantly decreased average

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**Table 1: Classification of topical peptides**

| Signal peptides | Structural peptides | Carrier peptides | Neurotransmitter-inhibitor peptides | Enzyme inhibitory peptide |
|-----------------|--------------------|-----------------|------------------------------------|--------------------------|

Indian Journal of Dermatology, Venereology, and Leprology  | January-February 2017  | Vol 83  | Issue 1
### Table 2: Commonly used peptides

| Type of peptide       | Site of action                                    | Name of peptide       | Mechanism of action                                                                 | Use as a cosmeceutical               |
|-----------------------|---------------------------------------------------|-----------------------|-------------------------------------------------------------------------------------|--------------------------------------|
| Signal peptide        | Modulator of dermal extracellular matrix          | Pal-KTTKS             | Increases synthesis of types I and type III collagen and fibronectin, elastin and glycosaminoglycan production | Anti-wrinkle                          |
|                       | Collagen modulators                               | Pal-GHK or Pal tripeptide 1 | Retinoic acid-like activity. Stimulates collagen and glycosaminoglycan synthesis | Anti-aging                            |
|                       |                                                   | Trifluoroacetyl Tripeptide-2 | ECM stimulation via MMP-1, 3, 9 inhibition Elastase inhibitor                               | Anti-aging                            |
|                       |                                                   | Palmitoyl tripeptide-3/5 | Mimics thrombospondin 1 tripeptide sequence and collagen synthesis via TGF-β          | Anti-wrinkle                          |
|                       |                                                   | Tripeptide-10          | Collagen fibrillogenesis and diameter and placement of collagen fibers. Mimics the sequences of decorin that binds to collagen fibrils | Anti-aging                            |
|                       |                                                   | Peptamide-6 or phe-val-ala-pro-phe-pro | It mimics the action of TGF-β which facilitates maturation of adipocyte precursor cells into contractile fibroblasts. Therefore, this prevents the differentiation of adipocytes | Skin firming agent in treatment of cellulite Anti-aging |
|                       |                                                   | Oligopeptide           | Inhibits enzyme procollagen-C proteinase which converts procollagen to collagen.       | Skin laxity                           |
|                       |                                                   | Tyr-Tyr-Arg-Ala-Asp-Ala | Stimulates collagen1 and lumican and syndecan synthesis                               | Anti-wrinkle                          |
|                       |                                                   | Gly-Glu-Lys-Gly        | Induces collagen production                                                          | Skin laxity                           |
|                       |                                                   | Acetyl tetrapeptide-5  | Edema reduction by ACE inhibition and collagen crosslinking. It inhibits glycation thereby preventing abnormal crosslinking of collagen fibers | Dermatochalasis or baggy eye lids     |
|                       |                                                   | Dipeptide-2/(valyl-tryptophane) | Lymph drainage via ACE inhibition                                                    | Baggy eyelids                         |
|                       | Elastin modulators                                | Hexapeptide            | Stimulates human skin fibroblasts, angiogenesis, endothelial cell migration and downregulates elastin | Skin laxity                           |
|                       |                                                   | Val-Gly-Val-Ala-Pro-Gly |                                                   | Anti-wrinkle                          |
|                       | Keratinocytes/epidermal cells                     | Palmitoyl oligopeptide | Increases collagen and hyaluronic acid                                               | Anti-aging                            |
|                       |                                                   | Aquaporin              | Increases the thickness of the stratum corneum                                       | Skin moisturizer                      |
|                       |                                                   | Growth factors         | TGF-α/TGF-β reversibly inhibit keratinocyte growth and are chemotactic for macrophages and fibroblasts promote neovascularization, promote cell growth | Wrinkles Post-skin resurfacing Photoaging |
|                       | Transforming growth factor                        | Heat shock protein 70  | Protects cell from apoptosis, aging and UV damage It inhibits aggregation and assists in the refolding of denatured proteins | Wrinkles Anti-aging                   |
|                       | VEGFs, hepatocyte growth factors, b-FGF          | Interferon alpha       | Increases the concentration of dendritic cells and CD1a and HLA-DR positive cells | Wrinkles Anti-aging                   |
|                       | Keratinocyte growth factor and insulin-like growth factor | Kinetin (natural plant derived growth hormone ) | Delays the onset of aging characteristics in human fibroblasts, inhibits keratinocyte growth | Wrinkles Anti-aging                   |

Contd...
Table 2: Contd...

| Type of peptide | Site of action | Name of peptide | Mechanism of action | Use as a cosmeceutical |
|-----------------|---------------|-----------------|---------------------|------------------------|
| Modulation of melanogenesis | Tetrapeptide (His-D-Phe-Arg-Trp) | Analogue of α-MSH induces melanin synthesis | Diminishes DNA damage by reducing the production of reactive oxidative species and enhancing repair of DNA photoproducts | Vitiligo, Cosmetic tanning |
| | Tripeptide (His-D-Phe-Arg) | Analogue of α-MSH induces melanin synthesis | | Vitiligo, Cosmetic tanning |
| | Ser-Tyr-Ser-Nle-Glu-His-D-p Phe-Arg-Trp-Gly-Lys-Pro-Val (Melano-Tan-I) | MC1R/α-MSH signaling pathway | Induces melanin synthesis | Vitiligo, Cosmetic tanning |
| | Decapeptide | Derived from b-FGF, induces melanin synthesis | | Vitiligo |
| | Acetyl hexapeptide-1 | Melanin increase via α-MSH regulation | | Vitiligo, Tanning, Hair repigmentation |
| | Tyr-Arg-Ser-Arg-Lys-Tyr-Ser-Trp-Tyr (decapetide-12) | Tyrosinase inhibitor | | Melasma, postinflammatory hyperpigmentation, Lentigo, Freckles |
| | Nonapeptide-1 | Tyrosinase activation inhibition | | Melasma, postinflammatory hyperpigmentation |
| Structural peptide | Keratin protein/ amino acids extracted from human hair or sheep’s wool | Improves hydration and elasticity of skin and hairs | | Skin and hair moisturizer, Hair shiner, Firming agent |
| Carrier peptide | Collagen and elastin synthesis | GHK-Cu glycy1-histidyl-lysine (tripeptide 1) | Potent activator of acute and chronic wound healing. Induces collagen remodeling by upregulating levels of MMP-2, TIMP-1 and TIMP-2 | Anti-aging, Skin laxity, Wrinkles, Post-skin resurfacing |
| | | Manganese tripeptide complex-1 GHK-Mn | Stimulates matrix protein growth, antioxidant responses and manganese-superoxide dismutase pathway | Wrinkles, Anti-aging |
| Neurotransmitter-inhibitor peptides | Acetyl hexapeptide 3/8 | Botox-like via SNARE inhibition and catecholamine release | | Periorbital wrinkle, skin moisturizer improves skin firmness and tone |
| | Pentapeptide 18 | Mimics the natural mechanism of enkephalins and inhibits neuronal activity and catecholamine release | | Periorbital wrinkle, skin moisturizer improves skin firmness and tone |
| | Pentapeptide 3 | Competitive antagonist at acetylcholine receptors | | Anti-wrinkle, Anti-aging |
| | Dipeptide diaminobutyroyl benzylamide diacetate (tripeptide 3) | Botox-like via acetylcholine receptor, mimics effect of waglerin, a neurotoxin found in the venom of the temple viper (Tropidolaemus wagleri) | | Anti-wrinkle, Anti-aging |
| Enzyme inhibitor peptide | Soybean amino acids | Inhibits proteinase formation, increases the length and number of hair roots | | Anti-aging, Skin moisturizer, Hair promoting agent |
| | Rice peptides | Matrix metalloproteinase activity | Induces expression of hyaluronan synthase 2 gene in keratinocytes | Anti-aging, Hair conditioning agent |

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Peptides modulating elastin

Elastic fibers are important components of the extracellular matrix and consist of two elements, the microfibrils and matrix elastin. Natural aging and excessive exposure to ultraviolet light cause degenerative changes within the elastin fiber meshwork.\(^3\)

Val-Gly-Val-Ala-Pro-Gly is a hexapeptide which is repeated multiple times in human, bovine and porcine elastin molecules.\(^3\) This peptide has a high degree of specificity towards elastin molecules and is involved in the autoregulation of elastin synthesis through a negative feedback mechanism.\(^2\) It is also a potent stimulator of human skin fibroblasts, angiogenesis and endothelial cell migration. Palmitoyl oligopeptide contains such a fragment of elastin and is incorporated into products to provide “reconstruction of the dermis” and produce “chemotaxis for restructuring and repair.”\(^3\)

Peptides affecting keratinocyte/epidermal cells

Aquaporin constitutes one family of transmembrane proteins derived from Ajuga turkestanica facilitating...
transport of water across the cell membrane. Aquaporins in keratinocytes are involved in cell migration and proliferation with consequences for the antimicrobial defense of the skin.

Aquaporin 3 is the predominant aquaporin in human skin. It is an aquaglyceroporin, i.e., it can co-transport glycerol along with water and its absence causes skin dryness and affects barrier function.[28]

A study conducted by Dumas et al. showed a significant decrease in transepidermal water loss in aquaporin-treated forearms versus untreated forearms.[29]

Growth factors are proteins that regulate cellular growth, proliferation and differentiation under controlled conditions. Several growth factors and cytokines used singly or in combination have been used to treat aging skin problems. Studies using these growth factors in combination showed a significant improvement in the wrinkle score as compared to placebo, when used for more than two months.[30,31]

Heat shock proteins protect protein substrates against conformational damage to promote the function of the protein and prevent aggregation and formation of toxic inclusion bodies. Aging alters the ability of cells to express Hsp70 in response to stress and any Hsp70 induction or application can reverse the process.[32-34]

Studies on both cultured human epidermal cells and ex vivo skin showed that induction or administration of Hsp70 before stress significantly diminished ultraviolet-related morphological changes and sunburn cell number.[9]

Interferon-α increases the concentration of dendritic cells and CD1a and HLA-DR-positive cells. Ghersetich and Lotti conducted a before-after study with three different inclusion protocols: five individuals aged 18–21 years, five aged 57–75 years and five aged 30–45 years under went cycles of psoralen plus ultraviolet A (PUVA) therapy over a year. Alpha-interferon cream (2,000,000 IU/day) in carboxymethylcellulose and glycerin was applied on the periauricular area 3 times a day for 4 weeks. Counts for cells that expressed CD-1 and HLA-DR were significant compared with baseline in aged and PUVA exposed volunteers.[35,36]

Studies on kinetin in patients with photodamaged skin revealed moderate to significant improvement in the color, epidermal thickness, wrinkling and skin texture.[37]

**Melanin modulating peptides**

Melanin protects nuclear DNA from harmful ultraviolet radiation and also acts as a free radical scavenger. Alteration of melanin (increase or decrease) results in cosmetic concerns.[3] The synthesis of melanin is regulated by the binding of the peptide, α-melanocyte-stimulating hormone to the melanocortin-1 receptor and the activation of tyrosinase enzyme.[3] Various analogs of α-melanocyte-stimulating hormone have been used in topical creams for photoprotection and preventing photocarcinogenesis. Among them, a tetrapeptide (His-D-Phe-Arg-Trp) and a tripeptide (His-D-Phe-Arg) are found to be more potent than α-melanocyte-stimulating hormone in stimulating the activity of tyrosinase and thus in melanogenesis, reducing apoptosis and release of hydrogen peroxide and enhancing repair of deoxyribonucleic acid photoproducts in melanocytes exposed to ultraviolet light.[38]

Decapeptide-12 (Tyr-Arg-Ser-Arg-Lys-Tyr-Ser-Ser-Trp-Tyr), a synthetic fragment of basic fibroblast growth factor has been found to competitively inhibit tyrosinase more potently than hydroquinone.[2] A split-face, double-blinded, placebo-controlled pilot study with topical decapeptide-12 cream at a concentration of 0.01% in five patients with recalcitrant melasma showed a 50% average improvement in pigmentation with no side effects after 4 months of treatment.[39] Ramaiah et al. studied the role of basic fibroblast growth factor in repigmentation in vitiligo and found significant improvement with therapy.[40]

**STRUCTURAL PEPTIDES**

Keratin is a major structural protein in the skin. Barba et al. studied wool-derived hydrolyzed keratin peptide (molecular weight <1000 Da) on skin in two different formulations, an aqueous solution and an internal wool lipids liposome suspension. Significant differences were found between the control and treated sites with the treated areas showing an increase in hydration and elasticity as a result of keratin peptide application.[41,42]

Keratin-peptides based on the fragment of hair keratin type II cuticular protein in water formulation was shown to improve the mechanical and thermal property of weakened hair.[43]
CARRIER PEPTIDES

Copper has an important role in enzymatic reactions associated with wound healing. It is a co-factor of lysyl oxidase and superoxide dismutase which are involved in collagen production and preventing free radical damage, respectively. Studies have found that the tripeptide glycyl-histidyl-lysine, a fragment of the alpha chain of collagen, possesses a high affinity for copper ions and forms the complex glycyl-histidyl-lysine-Cu.

In a double-blind, placebo-controlled study by Leyden et al. among 71 women volunteers with mild to advanced photodamage, significant improvement was noted in skin texture after 12 weeks. In another 12 week study conducted by Finkey et al., among 67 women with mild to advanced photodamaged skin, there was significant improvement in skin laxity and clarity with decreased wrinkles.

PEPTIDES MODULATING ACETYLCHOLINE TRANSMISSION

Injectable botulinum toxin treatments account for the largest number of cosmetic procedures in the United States with a 6% increase year-on-year. The current issues which may necessitate the use of topical botulinum toxin are pre-morbid psychosocial problems such as aversion and phobia to needles, fear of frozen face and pain.

Cutaneous nerve fibers release neurotransmitters which act on specific receptors on target cells in the skin inducing cell growth and differentiation, immunity and inflammation and tissue repair. Membrane fusion between vesicles and target membranes is an important step in these processes and is mediated by a large number of so-called soluble N-ethylmaleimide-sensitive factor attachment protein receptors. These soluble N-ethylmaleimide-sensitive factor attachment protein receptor complexes, specifically synaptosomal-associated protein 25 are targeted by botulinum toxin. Therefore, peptides that mimic the amino acid sequence of the synaptic protein synaptosomal-associated protein 25 were shown to be specific inhibitors of neurosecretion at micromolar concentration.

Botulinum neurotoxin type A has been designed for transdermal delivery using a patented translocating sequence technology where the peptide is carried to its target site via transcutaneous flux. Brandt et al. studied efficacy and safety of topical botulinum toxin gel in lateral canthal lines in healthy adult subjects. At 8 weeks, 50% showed a 2 point or greater improvement in baseline lateral canthal line severity (P < 0.001) with no treatment-related adverse events.

Acetyl hexapeptide-3 (Ac-Glu-Glu-Met-Gln-Arg-Arg-NH2) is a synthetic peptide derived from the N-terminal domain of the protein synaptosomal-associated protein-25. It modulates vesicle docking by interfering with the formation of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex necessary for catecholamine release from chromaffin cells. A study conducted by Blanes-Mira et al. in 10 volunteers with 10% acetyl hexapeptide-3 noted a 27% reduction in the depth of wrinkles after 30 days. Acetyl hexapeptide-3 has been shown to have similar potency as botulinum neurotoxin type A with respect to neurotransmitter release, but displayed lower efficacy.

Pentapeptide-3 acts as a competitive antagonist at the acetylcholine postsynaptic membrane receptor thereby preventing sodium ion channels from opening, thus inhibiting depolarization and muscle contraction. In vitro studies have demonstrated that pentapeptide-3 significantly reduces muscle cell contraction by 71% within 1 minute of application and 58% after 2 hours.

Enkephalins are endogenous opioids that inhibit neuronal activity by binding G-protein coupled inhibitory receptors thereby inhibiting acetylcholine release across the synapse to the muscle preventing muscle contraction. In vitro studies measuring the modulation of glutamate release in neuronal cell culture showed reduced neurotransmitter release. In vivo studies measuring anti-wrinkle activity using skin topography analysis of silicon imprints revealed decreased wrinkle depth.

Tripeptide-3 (beta-Ala-Pro-Dab-NH-benzyl) causes reversible antagonism of muscular nicotinic acetylcholine receptors at the post-synaptic membrane, preventing binding of acetylcholine to the receptors.
In vitro studies show that tripeptide-3 (0.5 mM) reduces muscle contraction and its action is reversible. An in vivo study showed up to 52% reduction in the appearance of wrinkle size in test volunteers after a 28-day application of a 4% formulation to the forehead, twice a day.[52]

**ENZYME INHIBITORY PEPTIDES**

Enzyme inhibitor peptides directly or indirectly inhibit an enzyme. Soy protein is an enzyme inhibitor peptide derived from soya bean seeds which inhibits proteinases. A study by Südel et al. in 21 healthy women who used soy extract and placebo creams on the volar aspect of forearms showed that papillae index was increased more by soy extract than placebo.[55,56]

Rice peptides are natural proteins that inhibit matrix metalloproteinase activity and induce expression of hyaluronan synthase 2 gene in keratinocytes.[56]

Zhaorigetu et al., in a study of silk peptides on 30 female hairless mice, noted that 5 mg of silk protein following exposure to ultraviolet B significantly inhibited the formation of skin lesions.[57]

The various advantages and disadvantages of peptides are given in Tables 3 and 4.[3,6,58]

**TRANSDERMAL DELIVERY OF OLIGOPEPTIDES**

Transdermal delivery of a drug involves its passage through the stratum corneum and later the dermis, into the circulation or the target site for action. Peptides pose challenges for passive transdermal delivery because they may be charged at physiological pH and there are various proteolytic enzymes capable of rapidly degrading oligopeptides.[52]

To overcome the stratum corneum barrier, several enhancement techniques have been used [Table 5].[52,59,60]

Penetration enhancers alter the lipid structure of the stratum corneum thereby reducing its barrier properties and increasing its permeability for drugs which would not pass through the skin passively. Various penetration enhancers include alcohols, azones, hexanoates, unsaturated fatty acids such as oleic acid, pyrrolidones, urea, sugar esters and surfactants.[52,59] This class of permeation enhancers has been shown to increase skin permeability by disordering or “fluidizing” the lipid structure of the stratum corneum and forming microcavities within the lipid bilayers which ultimately increase the diffusion coefficient of a drug. Care must be taken to choose a chemical enhancer that does not denature the peptide.[59]

Co-administration of certain peptide sequences, acting as peptide facilitators, has also been reported to increase peptide delivery. Co-administration of a short synthetic peptide increased passive delivery of insulin and human growth hormone.[59]

Chemical modification of peptides has also been tried to enhance drug delivery. Lipophilic derivatives of peptides have been reported to have better skin permeability.[59]

| Table 3: Advantages of peptides as cosmeceuticals[3,6,58] |
|----------------------------------------------------------|
| Peptides are involved in many natural processes with relevance to skin care, such as the modulation of cell proliferation, cell migration, inflammation, angiogenesis, melanogenesis and regulation and synthesis of proteins |
| Peptides are highly selective as they have multiple points of contact with their target. This results in decreased side effects and toxicity |
| Cosmeceuticals are not regulated by the US Food and Drug Administration and, thus, are not subject to pre-market requirements for proof of safety or efficacy |
| Peptides used primarily consist of natural L-amino acids which in general are not immunogenic and are readily broken down over time to yield individual natural amino acids |

| Table 4: Limitations of peptides as cosmeceuticals[3,8,58] |
|----------------------------------------------------------|
| Cosmeceutical products often are tested through in vitro studies using silicone replicas of skin. Clinical trials involving peptides are usually small, open-label studies which may be by the cosmetic companies themselves |
| The prices of peptides vary depending on the type and number of amino acids required as certain amino acids are more expensive as compared to others |
| Transdermal delivery and efficacy are a challenge as they tend to have high molecular weight, low lipophilicity, be bound by other ingredients preventing release from the formulation or in an active form |

| Table 5: Enhancement techniques for transdermal delivery of oligopeptides |
|----------------------------------------------------------|
| Penetration enhancers |
| Facilitating peptide sequences |
| Chemical modification of the peptide itself |
| Encapsulation of peptides |
| Other techniques such as iontophoresis, microneedling, sonophoresis, thermal ablation, jet injectors, electroporation and fractional photothermolysis |

Chemical modification of peptides has also been tried to enhance drug delivery. Lipophilic derivatives of peptides have been reported to have better skin permeability.[59]
Encapsulation of peptides has also been reported to increase peptide delivery across skin. Different types of particles such as liposomes, transfersomes, niosomes and ethosomes have been developed and investigated. The surfactants in the particles aid in local fluidization of the lipids that then allows for the particles to remain in the upper layers of the stratum corneum where they form a depot for a prolonged effect. Liposomes are composed of naturally occurring epidermal lipids; therefore, adverse effects do not seem likely as they are biodegradable, weakly immunogenic and non-toxic. Transfersomes are more elastic in nature which has been claimed to allow them to squeeze their way through the pores on the surface of skin into the deeper layers. Niosomes contain a bilayer of non-ionic surface active agent and ethosomes are phospholipid-based elastic nanovesicles with high content of ethanol.[62,59,60]

CONCLUSION

With an ever increasing aging population, the requirement of a suitable molecule with good anti-aging effects is becoming a necessity in the current scenario. Peptides form an important and useful option considering their natural availability, selective mode of action and low incidence of side effects. With increasing therapeutic use of commercial peptides and newer technological modifications in peptide pharmacokinetics and dynamics, the role of peptides as cosmeceuticals in various dermatological conditions appears promising.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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