International Multispecialty Journal of Health (IMJ Health)
ISSN: [2395-6291]
[Vol-12, Issue-7, July- 2026]
Website: www.imjhealth.org
Journal DOI: 10.25125/medical-journal

Peptide-Based Approaches for Extracellular Matrix Remodeling, Senescence Modulation, and Topical Delivery in Adult and Aging Skin

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Received:-03 July 2026/ Revised:- 11 July 2026/ Accepted: 21 July 2026/ Published: 31-07-2026

Abstract**—** *This study synthesizes current knowledge on bioactive peptides for adult and aging skin, integrating skin structure, aging biology, peptide classes, formulation science, preclinical models and clinical evaluation to inform evidence-based topical strategies. Skin architecture and ageing mechanisms are summarized to contextualize peptide interventions that target epidermal renewal, dermal extracellular matrix, pigmentation and inflammation. Peptide categories covered include signal peptides that promote collagen, elastin and glycosaminoglycan synthesis, carrier peptides that deliver trace metals such as copper, neurotransmitter-modulating peptides for expression lines, and enzyme-inhibiting sequences that reduce MMP and tyrosinase activity. Case examples describe Pal-KTTKS, Pal-GHK, Cu-GHK, tripeptide-10 citrulline, SA1-III (KP1) and Pep 14, highlighting modes of action from collagen fibrillogenesis control and MMP activity reduction to modulation of PP2A/AKT and senescence-associated signaling. Formulation considerations examine physicochemical constraints on cutaneous delivery, lipidation strategies, nanocarriers, cell-penetrating peptides, stability challenges and vehicle design that balance penetration with safety. Mechanistic assays spanning fibroblast and keratinocyte monolayers, 3D skin equivalents and ex vivo human skin are presented alongside clinical and instrumental endpoints including profilometry, ultrasound, histology and DNA methylation age metrics. Safety, sensitization, regulatory labeling and claim frameworks are discussed with recommendations for rigorous trial design, standardized measurements and population-specific risk assessment for aging skin. Practical guidance addresses regimen sequencing, combination with retinoids and procedures such as laser, microneedling and fillers, emphasizing controlled evaluation to optimize matrix remodeling, repair and tolerability in mature skin.*

Keywords— Anti-aging, Dermatology, Peptide, Skincare, Extracellular Matrix, Senescence.

I. INTRODUCTION

Adult and aging skin comprises discrete yet tightly interconnected layers with specialized cell populations and extracellular matrices that are directly relevant to peptide-based interventions. The outer compartment, the epidermis, is a stratified epithelium populated primarily by keratinocytes. Its innermost portion contains proliferating basal keratinocytes, above which lie three differentiated strata: stratum spinosum, stratum granulosum and stratum corneum. The most superficial stratum corneum consists of anucleate corneocytes embedded in a lipid-rich matrix, a configuration that is central to barrier function and to the limitation of transcutaneous penetration of many hydrophilic molecules [1].

Epidermal renewal depends on distinct epidermal stem cell populations distributed within the basal layer and the hair follicle. These stem cells support continuous regeneration of the epidermis on top of the collagen-rich dermal extracellular matrix (ECM). The dermis lies beneath the basal epidermal layer and contains vasculature and adnexal structures within an ECM produced by dermal fibroblasts, which are terminally differentiated cells of mesenchymal origin. Collagen and elastin fibers within this matrix provide mechanical integrity, firmness and tensile strength, and are key targets of aging-associated

degradation processes. Histologic and molecular analyses of photoaged skin show dermal loss of collagen and elastin accompanied by increased dermal inflammation and elevated gene expression of matrix metalloproteinases (MMPs), with concomitant decreases in ECM components such as collagen and elastin [1,2,3].

Extrinsic aging driven by ultraviolet (UV) radiation particularly affects epidermal and dermal structure. UVB, with higher energy and shorter wavelength, primarily damages the epidermis through direct absorption by chromophores including nucleic acids and amino acids, leading to the formation of cyclobutane pyrimidine dimers and photoproducts. These lesions interfere with RNA transcription, activate p53, and induce keratinocyte apoptosis. Photosensitization mechanisms further generate reactive oxygen species (ROS) and reactive nitrogen species that penetrate nuclei and induce oxidative DNA damage and strand breaks. Downstream, oxidative stress activates inflammatory pathways and upregulates MMPs such as MMP-1, MMP-3 and MMP-9, which degrade collagen and elastin, with clinical consequences including wrinkle formation, loss of elasticity, hyperpigmented lesions and impaired barrier function [3].

Within the dermal ECM, fragmented collagen acquires a central role in propagating aging-related signaling. Photoaging is strongly associated with collagen degradation initiated by UV-induced increases in MMP secretion from basal keratinocytes and dermal fibroblasts, linked to activation of AP-1 signaling. In vitro, dermal fibroblasts cultured on synthetically degraded collagen exhibit increased ROS generation, elevated MMP secretion and reduced collagen production. Co-culture experiments show that MMP expression in fibroblasts decreases regenerative capacity and longevity of overlying epidermal stem cells, highlighting bidirectional communication between dermal ECM and epidermal progenitors. These interactions position ECM composition and integrity as critical determinants of both structural and functional aspects of skin aging, including barrier maintenance and repair potential [1].

Structural differences between intrinsically aged and photoaged skin further clarify how tissue architecture underlies clinical phenotypes. Intrinsic aging typically presents with fine wrinkles, some deepening of surface markings, modest loss of elasticity, and relatively smooth but sagging skin. Photoaged skin, in contrast, shows nodular, leathery surfaces, coarse wrinkles, severe loss of elasticity, yellowish mottled pigmentation and a reddened appearance. At the epidermal level, intrinsic aging involves thinning with lower cell growth and minor keratinocyte irregularities, while photoaging is characterized by marked acanthosis followed by cellular atrophy, high basal keratinocyte irregularity, a compact stratum corneum and loss of rete pegs in both states. In the dermis, intrinsic aging features a thinner reticular dermis with decreased fibroblasts and collagen fibers, whereas photoaging produces a thickened dermis with elastosis, increased and hyperactive fibroblasts and mast cells, excessive and disorganized elastin, collagen fiber thickening followed by wear, and formation of a grenz zone associated with solar elastosis. Collagen bundles are thick but disoriented in intrinsic aging, and markedly decreased in photoaging, while glycosaminoglycans are slightly decreased versus markedly increased, respectively. Microvascular loss is moderate in intrinsic aging but pronounced, abnormal and telangiectatic in photoaging [2].

These structural and functional characteristics of epidermis, dermis and ECM set the biological context in which signaling peptides must operate, including constraints imposed by the stratum corneum barrier and the central role of fibroblast–matrix–stem cell interactions in maintaining adult skin homeostasis and responding to injury and photoinduced damage [1,2,3].

Cosmetic use of peptides has expanded markedly, with a wide variety of structures now incorporated into anti-aging formulations targeted to adult and aging skin. These compounds are generally short chains of amino acids, often chemically synthesized or obtained by biotechnology, and are selected or modified to display specific biological activities relevant to skin appearance and function. Within topical products, peptides can be present as isolated molecules, as components of protein hydrolysates categorized as Generally Recognized as Safe (GRAS) by regulatory authorities, or embedded in complex mixtures whose individual contributions to efficacy are not always clear [4,5].

A central conceptual framework classifies cosmetic peptides by their predominant mechanism of action. Signal peptides stimulate production of extracellular matrix molecules such as collagen, elastin, proteoglycans, glycosaminoglycans and fibronectin, and may enhance cell growth and other metabolic functions. Carrier peptides facilitate transport or stabilization of trace elements like copper and manganese inside cells. Neurotransmitter-inhibiting peptides target expression wrinkles by modulating acetylcholine release or related neuronal mechanisms, whereas enzyme-inhibiting peptides reduce the activity of proteases involved in skin aging, including matrix metalloproteinases and tyrosinase [4,6,7,8].

This mechanistic categorization underpins formulation choices for specific clinical indications such as wrinkles, sagging, hyperpigmentation and photo-damage. Signal peptides are particularly relevant for aging skin because they modulate collagen turnover and broader matrix homeostasis. Examples include palmitoyl pentapeptide Pal-KTTKS, a fragment of procollagen I that stimulates collagen types I, III and VI, fibronectin, elastin and glucosaminoglycan production, and is frequently used as an anti-wrinkle and anti-aging topical agent. Palmitoyl tripeptide-1 (Pal-GHK) and its unconjugated form GHK act as collagen-modulating signal peptides, increasing collagen and glycosaminoglycan synthesis in vitro and in vivo. Palmitoyl tripeptide-3/5 mimics a thrombospondin I sequence to activate transforming growth factor-β and thereby promote collagen formation, and is formulated as a firming, moisturizing and anti-wrinkle agent, including for stretch marks. Tripeptide-10 citrulline, a decorin-mimetic, regulates collagen fibrillogenesis and controls fibril diameter and placement, conferring firming and anti-aging effects and utility as a sun protection agent. Synthetic acetyl tetrapeptides such as AcTP1 and AcTP2 further exemplify signal peptides that stimulate collagen I, lumican, keratinocyte growth and syndecan-1 synthesis, with anti-aging and firming applications [6,7,8,9].

Carrier peptides conceptually combine signaling and metal delivery functions. The copper tripeptide complex Cu-GHK, derived from the Gly-His-Lys sequence, is a well-examined example that stabilizes and transports copper while acting as a signal peptide. It supports tissue remodeling by promoting regular synthesis of collagen, elastin, proteoglycans and glycosaminoglycans, enhancing growth and migration of multiple cell types, and exerting anti-inflammatory and antioxidant responses. Topically, Cu-GHK is used in anti-aging, anti-wrinkle, after-sun and skin renewal products, moisturizers and hair growth stimulators. Clinical and experimental studies report increased keratinocyte proliferation, improved skin firmness, elasticity, thickness, wrinkle reduction and diminished hyperpigmentation, as well as stimulation of dermal procollagen synthesis superior to vitamin C or retinoic acid in comparative trials [4,7,9].

Neurotransmitter-inhibiting peptides in cosmetic formulations conceptually target dynamic expression lines by modulating neuromuscular signaling without the invasiveness of injectable toxins. Acetyl hexapeptide-3 (also known as acetyl hexapeptide-8) inhibits SNARE complex formation and catecholamine release, leading to reduced muscle contraction and is marketed for periorbital wrinkles, skin moisturization and improved firmness and tone. Pentapeptide-18 mimics enkephalin mechanisms to inhibit neuronal activity and catecholamine release, and pentapeptide-3 acts as a competitive antagonist at acetylcholine receptors as an alternative to botulinum toxin for expression wrinkles. These molecules illustrate how peptide design can exploit neuromodulatory pathways while remaining within cosmetic claim boundaries focused on appearance [4,5,9].

Despite an extensive catalog of peptide ingredients, research sources note that in vivo efficacy data for many cosmetic peptides remain limited, and mixtures in commercial formulations complicate attribution of clinical effects to individual molecules. Consequently, conceptual discussions emphasize the need to define modes of action, optimize study designs and clarify mechanistic and receptor-level interactions for peptides intended for adult and aging skin care [4,6,7].

TABLE 1
CLASSIFICATION OF PEPTIDES IN SKINCARE

Peptide Class	Mechanism of Action	Key Examples	Primary Indications
Signal Peptides	Stimulate ECM production (collagen, elastin, GAGs)	Pal-KTTKS, Pal-GHK, Palmitoyl tripeptide-3/5, Tripeptide-10 citrulline, AcTP1, AcTP2	Wrinkles, sagging, loss of firmness
Carrier Peptides	Transport trace metals (Cu, Mn) with signaling functions	Cu-GHK (Copper tripeptide)	Tissue remodeling, wound healing, anti-aging
Neurotransmitter-Inhibiting Peptides	Modulate neuromuscular signaling	Acetyl hexapeptide-3/8, Pentapeptide-18, Pentapeptide-3	Expression lines, periorbital wrinkles
Enzyme-Inhibiting Peptides	Reduce MMP and tyrosinase activity	SA1-III (KP1), Rice-derived peptides	Collagen preservation, pigmentation control

Source: Compiled from [4,6,7,8,9]

II. METHODOLOGY

2.1 Search Strategy

A comprehensive literature search was conducted using systematic protocols. Electronic databases searched included PubMed, Google Scholar, MEDLINE, Scopus, and Web of Science. The search covered publications from January 2000 to April 2024. Search terms were organized around the following conceptual axes:

A. Peptide types and mechanisms: ("bioactive peptides" OR "signal peptides" OR "carrier peptides" OR "neurotransmitter-inhibiting peptides" OR "enzyme-inhibiting peptides" OR "cosmetic peptides" OR "anti-aging peptides")

B. Skin biology and aging: ("skin aging" OR "cutaneous aging" OR "photoaging" OR "extracellular matrix" OR "collagen" OR "elastin" OR "senescence" OR "fibroblast" OR "keratinocyte")

C. Formulation and delivery: ("topical delivery" OR "formulation" OR "nanocarrier" OR "lipidation" OR "cell-penetrating peptide" OR "stratum corneum" OR "permeation")

D. Evaluation and clinical studies: ("clinical trial" OR "in vitro" OR "ex vivo" OR "profilometry" OR "ultrasound" OR "methylation age" OR "safety" OR "irritation")

Boolean operators (AND, OR) were used to combine search terms. Reference lists of included articles were also screened for additional relevant publications.

2.2 Eligibility Criteria

Retrieved papers were screened by title, abstract, and full text against defined eligibility criteria. Included were:

- Peer-reviewed original research articles (randomized controlled trials, non-randomized studies, in vitro and ex vivo studies)
- Systematic reviews and meta-analyses
- Authoritative reviews in dermatological, cosmetic, or pharmacological journals
- Studies published in English
- Exclusion criteria encompassed:
- Studies on injectable or systemic peptide therapies (outside topical applications)
- Studies on peptides for non-cutaneous indications
- Conference abstracts without full text
- Studies lacking clearly defined methodology or outcomes
- Self-administered questionnaire surveys without objective measurements

2.3 Quality Assessment

Quality assessment of included studies was performed using appropriate tools: Cochrane Risk of Bias for randomized controlled trials, Newcastle-Ottawa Scale for observational studies, and a custom quality checklist for in vitro and ex vivo studies. Evidence was graded according to the strength and consistency of available data, with priority given to well-designed clinical trials and studies with objective, validated endpoints.

2.4 Data Extraction and Synthesis

Extracted data included: peptide characteristics (type, sequence, concentration, vehicle), study design (in vitro, ex vivo, clinical), participant demographics (where applicable), intervention regimens, outcome measures, and key findings. Given the heterogeneity of study designs, peptide types, and outcome measures, findings were synthesized narratively. Evidence was organized thematically according to the main areas of investigation: peptide classification, mechanisms of action, formulation strategies, evaluation methods, and clinical applications.

III. BIOLOGY AND PATHOPHYSIOLOGY OF SKIN AGING

3.1 Intrinsic Aging Mechanisms

Intrinsic aging in adult skin is characterized by coordinated structural and molecular changes affecting epidermis, dermis, vasculature and adnexal structures. Clinically, intrinsic aging presents with skin thinning, dryness, loss of elasticity and fine wrinkling, accompanied by impaired barrier function, delayed wound healing, cutaneous immunosenescence, dysregulated vasomotor responses, altered glandular secretions, sensory changes and reduced capacity for vitamin D synthesis. Histologic correlation includes thinning and flattening of the dermoepidermal junction, which decreases the contact surface area between epidermis and dermis and contributes to the fragile skin phenotype described as dermatoporosis, cutaneous insufficiency or skin failure. This phenotype reflects compromised regenerative capacity and structural maintenance in advanced intrinsic aging [3].

At the molecular level, telomere shortening is a central mechanism of chronological skin aging. Telomeres at chromosome termini prevent degradation and fusion, and their progressive shortening signals malfunction of this protective system. Shortened telomeres activate the DNA damage response pathway and downstream cyclin-dependent kinase inhibitors p16 and p21, leading to cell cycle arrest and cellular senescence. Intrinsic aging-induced senescence arising from repeated cell division is therefore directly attributed to gradual telomere erosion in cutaneous cells, with specific relevance to fibroblast and keratinocyte populations that support tissue homeostasis [1,3].

Oxidative stress represents another key driver. Reactive oxygen species generated during mitochondrial aerobic metabolism influence chronological aging by disrupting transmembrane signaling, inducing DNA damage and increasing expression of tumor necrosis factor alpha and matrix metalloproteinases. These zinc-containing metalloproteinases degrade extracellular matrix molecules and diminish collagen synthesis. Elevated ROS levels also oxidize cellular lipids, proteins and DNA, producing cellular dysfunction and oxidative protein damage as a primary biomarker of aging. In photodamaged epidermis, accumulation of lipofuscin, a redox-active aggregate, forms age spots and promotes cycles of free radical generation and proteasome inhibition that further favor protein aggregation [2,3].

Genetic determinants modulate intrinsic aging trajectories. Specific genes regulate cellular repair, responses to oxidative stress and synthesis of structural proteins such as collagen and elastin, and many exhibit pleiotropy, influencing multiple phenotypic traits. Single-nucleotide polymorphisms cluster within a set of central pleiotropic genes and pigmentation-associated genes, several located in chromosomal band 16q24.3. Transcriptomic analyses show that most aging-related genes are differentially expressed with age, linking gene expression profiles to cutaneous aging [3].

Hormonal alterations overlay these genetic influences. Declining estrogen during menopause affects skin because of nuclear estrogen receptor isoforms expressed in sebaceous and eccrine glands, dermal fibroblasts, sebocytes, adipocytes, melanocytes and keratinocytes. Reduced estrogen correlates with decreased collagen synthesis, diminished hydration and increased wrinkle formation, leading to dryness, thinning and elasticity loss in postmenopausal skin. In men, age-related testosterone decline similarly reduces skin thickness and sebum production, contributing to drier, less elastic skin, albeit generally less pronounced than estrogen-related changes. Additional hormones such as growth hormone and dehydroepiandrosterone also decrease with age, reducing cellular regeneration, repair and sebum production, and thereby increasing dryness, elasticity loss, impaired tissue regeneration and diminished UV protection [3].

Locally produced insulin-like growth factor 1 is reduced in senescent dermal fibroblasts, promoting connective tissue atrophy and aged skin phenotype. IGF-1 deficiency decreases epidermal proliferation and differentiation, impairs barrier function and relieves inhibition on matrix metalloproteinases, further favoring ECM degradation. Metabolic slowing augments these processes by limiting energy and nutrient supply, impairing cellular function and regenerative capacity, and delaying waste removal. Accumulation of damaged proteins and lipids and formation of advanced glycation end products cross-link collagen fibers, stiffen the matrix and reduce elasticity [3].

3.2 Extrinsic Aging and Photoaging Mechanisms

Extrinsic aging encompasses environmentally driven alterations in skin structure and function, with chronic solar radiation as a principal determinant. Ultraviolet radiation constitutes a small but biologically potent fraction of solar energy, comprising UVA (320–400nm) and UVB (280–320nm), which reach the Earth's surface, while UVC is largely absorbed by the ozone

layer. Immediately adjacent to UVA lies visible blue light (400–490nm), originating from sunlight and artificial sources such as LEDs and electronic screens, and increasingly scrutinized because of its cumulative facial exposure. Wavelength and energy profile govern penetration depth and target structures: UVA penetrates more deeply into the dermis and is strongly implicated in photoaging, while the higher-energy, shorter-wavelength UVB primarily affects the epidermis [3].

UV photons damage skin through direct absorption by chromophores and through photosensitization mechanisms. In direct absorption, nucleic acids and amino acids such as tryptophan and tyrosine act as chromophores that convert UV energy into molecular events, notably formation of cyclobutane pyrimidine dimers and 6-4 photoproducts in DNA. These lesions interfere with RNA transcription, activate p53, and drive keratinocyte apoptosis. Photosensitization generates reactive oxygen species and reactive nitrogen species from endogenous or exogenous sensitizers, leading to oxidative DNA damage and strand breaks. Resulting oxidative stress initiates inflammatory signaling and upregulates matrix metalloproteinases, particularly MMP-1, MMP-3 and MMP-9, which degrade collagen and elastin, reducing skin firmness and disturbing the extracellular matrix. Clinically, these processes manifest as loss of elasticity, wrinkle formation, hyperpigmented lesions and impaired barrier function, and underlie the morphological, histologic and biochemical changes collectively termed photoaging [2,3].

Visible blue light shares several mechanistic features with UVA. In vitro, blue light within 450–490nm exerts cytotoxic effects on human dermal fibroblasts and keratinocytes at high intensities, acting through chromophores such as flavin adenine dinucleotide and flavoproteins that trigger UVA-like photoreactions. At lower intensities, blue light reduces antimicrobial peptide expression, slows epidermal regeneration, compromises skin integrity, decreases cell viability and increases epidermal inflammatory markers. Blue light also stimulates melanogenesis through the G-protein-coupled receptor opsin-3; in darker phototypes, sustained tyrosinase activity and associated protein complexes produce prolonged hyperpigmentation. UVA1 further contributes to pigmentary change via immediate and persistent pigment darkening and delayed tanning, with visible light implicated in rapid, photochemical pigmentation and delayed neomelanogenesis. These pigmentary responses intersect with oxidative stress, as α-melanocyte-stimulating hormone reduces UV-induced hydrogen peroxide in melanocytes, suggesting a coupling between melanogenesis and ROS modulation [3].

Repetitive UV exposure leads to characteristic clinical features of photoaging, including fine and coarse wrinkles, solar elastosis, pigmentation disorders, lentigines, actinic keratoses, telangiectasia, laxity, roughness, extreme dryness and premalignant lesions. Histologically, solar lentigines show basal layer hyperpigmentation and irregular melanosome distribution driven by melanocytic hyperplasia induced by UV, visible light and other environmental factors. Solar elastosis reflects dermal thickening with abnormal elastotic material, associated with chronic ROS generation and MMP-9 and MMP-12 activation. Telangiectasias represent dilated superficial capillaries; proposed mechanisms include UV-induced downregulation of angiogenesis inhibitors such as thrombospondin-1 and increased nitric oxide production that perpetuates vasodilation [2,3].

3.3 Broader Exposome Contributions

Extrinsic aging is further shaped by the broader exposome, including pollution, smoking, diet, sleep and additional radiation sources. Environmental pollutants such as nitrogen dioxide, particulate matter and traffic-related emissions correlate with wrinkles and lentigines, likely through synergistic enhancement of ROS with UV. Ozone, despite limited penetration, oxidizes stratum corneum lipids and proteins, depletes antioxidants including vitamins C and E, activates NF-κB and increases interleukin-8, MMP-9 and COX-2, thereby reducing type I and III collagen and accelerating aging. Smoking delivers thousands of toxic compounds and is dose-dependently linked to premature wrinkling, solar elastosis-like elastic fiber changes, upregulation of MMP-1 and MMP-3, reduced transforming growth factor-β1 signaling, microvascular constriction, DNA mutations and chronic oxidative stress [2,3].

Dietary habits modulate collagen and elastic fibers, with processed sugars promoting abnormal glycation and cross-linking of collagen, and excessive lipid intake fostering a pro-inflammatory milieu with elevated tumor necrosis factor alpha and inflammasome activation. In contrast, omega-3 and omega-6 polyunsaturated fatty acids show anti-inflammatory and photoprotective effects in vitro, and vitamins C and E jointly support antioxidant defense, collagen synthesis and reduction of UV-induced lipid oxidation [2,3].

IV. MOLECULAR ACTIONS OF PEPTIDES IN CUTANEOUS TISSUES

Regulation of the extracellular matrix in aging skin can be directly modulated by several classes of bioactive peptides that act on collagen turnover, fibrillogenesis and metalloproteinase activity. Signal peptides derived from collagen or decorin sequences are particularly relevant, as they engage dermal fibroblasts to adjust production and organization of matrix components. Palmitoyl pentapeptide Pal-KTTKS, a fragment of procollagen I, stimulates synthesis of collagen types I, III and VI, as well as fibronectin, elastin and glucosaminoglycans, thereby addressing the age-related decline in these structural proteins and contributing to firmer, smoother skin with reduced fine lines and wrinkles [6,7,9].

Palmitoyl tripeptide-1 (Pal-GHK) similarly promotes collagen and glycosaminoglycan synthesis in vitro and in vivo, supporting its use as an anti-aging, anti-wrinkle, firming and moisturizing ingredient. Palmitoyl tripeptide-3/5 mimics a thrombospondin I tripeptide sequence, binds the inactive form of transforming growth factor-β and induces its activation, which in turn promotes collagen formation and is exploited in formulations targeting stretch marks and dermal firmness [6,7,9].

Beyond stimulating collagen production, some peptides modulate the qualitative architecture of fibrils. Tripeptide-10 citrulline, designed as a decorin-mimetic, binds collagen fibrils, regulates fibrillogenesis and influences fibril diameter and placement, which translates into firming and anti-aging effects and additional utility as a sun protection agent. By impacting fibril uniformity and growth, this peptide addresses changes in collagen organization that accompany aging and photo-damage [6,7,9].

Synthetic acetyl tetrapeptides also intervene in matrix homeostasis: acetyl tetrapeptide-9 (AcTP1) stimulates collagen I and lumican synthesis, whereas acetyl tetrapeptide-11 (AcTP2) increases keratinocyte growth and syndecan-1 synthesis, effects that enhance dermal structure and epidermal-dermal cohesion in anti-wrinkle and firming applications. These molecules belong to a broader group of matricins or collagen stimulators released from or modeled on extracellular matrix fragments that trigger signaling cascades leading to increased collagen, elastin, proteoglycan, glycosaminoglycan and fibronectin production, with downstream reductions in pigmentation of photo-damaged skin and improvement of wrinkles and elasticity [6,7,9].

Carrier peptides add a complementary layer of dermal remodeling by combining metal delivery with signaling functions. The copper tripeptide complex Cu-GHK (copper Gly-His-Lys) is described as both a signal and carrier peptide that promotes regular synthesis of collagen, elastin, proteoglycans and glycosaminoglycans, while providing anti-inflammatory and antioxidant responses relevant to matrix preservation under oxidative stress. In vitro experiments show that Cu-GHK increases collagen and glycosaminoglycan synthesis and other extracellular matrix molecules, and placebo-controlled clinical trials demonstrate stimulation of dermal procollagen synthesis that is significantly superior to vitamin C, tretinoin or melatonin. In a comparative study, topical Cu-GHK increased collagen in 70% of treated women, compared with 50% for vitamin C and 40% for retinoic acid, and longer-term applications in aged and sun-damaged skin improved density, thickness, elasticity, humidity and wrinkle smoothing via enhanced collagen synthesis. More generally, GHK and related complexes degrade extra-large collagen aggregates in scars, support regular collagen synthesis in normal skin, and promote elastin, proteoglycan and glycosaminoglycan production, alongside growth and migration of multiple cell types and anti-inflammatory and antioxidant activities. These properties directly support tissue remodeling and barrier reinforcement in adult and aging skin [4,7,9].

A distinct strategy for extracellular matrix regulation involves modulating collagen degradation rather than biosynthesis. SA1-III (KP1), a decapeptide derived from the C-terminal portion of serpin A1, has been characterized as a collagen turnover modulating peptide. In human dermal fibroblast cultures, SA1-III increases extracellular soluble collagen levels to an extent comparable with L-ascorbic acid and transforming growth factor-β1. Mechanistic analysis using Western blot and gelatin zymography demonstrates that this increase arises primarily from reduced collagen degradation, with minimal effect on biosynthesis or cell proliferation. Specifically, SA1-III decreases activity of MMP-2 and MMP-9 in cell-conditioned media without altering gene expression of inflammatory mediators in resting or lipopolysaccharide-stimulated fibroblasts. Acting at low concentrations and across fibroblasts from individuals of different ages, SA1-III thus protects collagen from enzymatic breakdown while avoiding pro-proliferative or pro-inflammatory effects, positioning it as a candidate for preserving matrix integrity in aging dermis [6].

TABLE 2
KEY PEPTIDES AND THEIR MECHANISMS OF ACTION

Peptide	Class	Sequence/Structure	Mechanism	Key Effects
Pal-KTTKS	Signal	Palmitoyl-Lys-Thr-Thr-Lys-Ser	Procollagen I fragment	Stimulates collagen I, III, VI, fibronectin, elastin, GAGs
Pal-GHK	Signal	Palmitoyl-Gly-His-Lys	Collagen fragment	Stimulates collagen and GAG synthesis
Cu-GHK	Carrier/Signal	Copper-Gly-His-Lys	Copper delivery + signaling	Stimulates collagen, elastin, GAGs; anti-inflammatory
Tripeptide-10 citrulline	Signal	Decorin-mimetic	Regulates fibrillogenesis	Controls fibril diameter and placement
AcTP1	Signal	Acetyl tetrapeptide-9	Lumican synthesis	Stimulates collagen I and lumican
AcTP2	Signal	Acetyl tetrapeptide-11	Syndecan-1 synthesis	Stimulates keratinocyte growth
SA1-III (KP1)	Enzyme-inhibiting	Serpin A1-derived	MMP-2/9 inhibition	Reduces collagen degradation
Acetyl hexapeptide-3/8	Neurotransmitter-inhibiting	Acetyl-Glu-Glu-Met-Gln-Arg-Arg	SNARE inhibition	Reduces muscle contraction

Source: Compiled from [4,6,7,9]

V. TYPES AND SOURCES OF PEPTIDES FOR SKINCARE FORMULATIONS

Synthetic and bioengineered peptides used in skincare are typically short amino acid chains whose sequences and chemical modifications are designed to achieve specific cutaneous functions, including improved skin penetration, receptor binding, stability and solubility. Modern approaches allow tailoring of these properties so that peptides can better traverse the stratum corneum, particularly in dry or aged skin, and interact with defined molecular targets in the epidermis and dermis [5,7].

Several families of synthetic signal peptides have been developed to stimulate extracellular matrix production. Palmitoyl pentapeptide Pal-KTTKS is a pro-collagen I fragment that stimulates collagen types I, III and VI, fibronectin, elastin and glucosaminoglycan production, and is frequently used as an anti-wrinkle and anti-aging topical agent. Its design includes five amino acids linked to a 16-carbon aliphatic chain, which improves permeability through the lipid matrix of the skin [6,7,9].

Palmitoyl tripeptide-1 (Pal-GHK) consists of the Gly-His-Lys collagen fragment conjugated to palmitic acid and has been shown in vitro and in vivo to stimulate collagen and glycosaminoglycan synthesis, supporting anti-aging, anti-wrinkle, firming and moisturizing actions in cosmetic products. Palmitoyl tripeptide-3/5 mimics a thrombospondin I tripeptide, binds inactive transforming growth factor-β and promotes its activation, thereby enhancing collagen formation; it is formulated as a firming, moisturizing and anti-wrinkle agent, including for stretch marks [6,7,9].

Tripeptide-10 citrulline, a decorin-mimetic peptide, regulates collagen fibrillogenesis and influences fibril diameter and placement, conferring anti-aging, firming and sun-protection properties. Synthetic acetyl tetrapeptides such as AcTP1 and AcTP2 further exemplify signal peptides: AcTP1 stimulates collagen I and lumican synthesis, while AcTP2 stimulates keratinocyte growth and syndecan-1 synthesis, with both used as anti-wrinkle and firming ingredients [6,7,9].

Carrier peptides represent another important synthetic class. Copper tripeptide complex Cu-GHK (copper Gly-His-Lys) is a well-examined molecule that acts both as signal and carrier peptide. It promotes regular synthesis of collagen, elastin, proteoglycans and glycosaminoglycans, and provides anti-inflammatory and antioxidant responses. Experimental work shows that Cu-GHK increases collagen, glycosaminoglycans and other extracellular matrix molecules in vitro. Placebo-controlled clinical trials demonstrate that topically applied Cu-GHK stimulates dermal procollagen synthesis significantly more than vitamin C, tretinoin or melatonin, with one study reporting increased collagen production in 70% of women treated with Cu-GHK versus 50% with vitamin C and 40% with retinoic acid. Additional studies in aged and sun-damaged skin showed improved density and thickness, elasticity, humidity, wrinkle smoothing and overall appearance after Cu-GHK cream application [4,7,9].

Synthetic neurotransmitter-inhibiting peptides are designed to act on neuromuscular signaling to reduce expression lines. Acetyl hexapeptide-3 (Acetyl hexapeptide-8, Argireline) inhibits SNARE complex formation and catecholamine release, and is used particularly for periorbital wrinkles, skin moisturization and improved firmness and tone. Pentapeptide-18 (Leuphasyl) mimics enkephalin mechanisms to inhibit neuronal activity and catecholamine release, while pentapeptide-3 (Vialox) functions

as a competitive antagonist at acetylcholine receptors and is positioned as a topical alternative to botulinum toxin for expression wrinkles. These peptides exemplify rational design of synthetic sequences to target specific neuronal pathways within the constraints of cosmetic indications [7,9].

Bioengineered peptides produced by biotechnological processes complement chemically synthesized molecules. Peptamide-6, generated by Saccharomyces yeast fermentation, is a firming signal peptide that increases collagen synthesis and upregulates growth factors, transmembrane, matrix and cell-shock proteins, making it suitable for face, body and eye creams. Recombinant human growth hormone is another biotechnological peptide classified as a signal peptide; it increases IGF-1 production, enhances fibroblast and keratinocyte activity and sebum production, and is used in anti-aging, anti-wrinkle and post-resurfacing formulations. More broadly, protein hydrolysates containing bioactive peptides are recognized as safe and are employed for skin moisturization and anti-aging applications, while biomimetic peptides produced in transformed bacteria systems have been explored to modulate dermal repair markers such as type I procollagen and AP-1 in vitro and in vivo [4,7,10].

Naturally derived peptides for skincare originate from plant, marine and animal sources, often obtained by controlled digestion or hydrolysis of structural or storage proteins. These peptide mixtures and isolated sequences can display anti-aging, antioxidant, whitening, moisturizing and repair-promoting activities that are relevant for adult and aging skin, but available data are uneven and frequently limited to small studies or in vitro models [2,7,11].

Plant-derived peptides include soybean, rice and cereal peptides. A pseudo-randomized in vivo/in vitro study in 10 women reported that a soybean peptide significantly increased glycosaminoglycan and collagen synthesis, supporting its anti-aging potential; this peptide is classified as an enzyme-inhibitor in cosmetic taxonomy, although the detailed mechanism is not fully defined. Rice-derived peptides have been studied in several forms. After special processing of rice bran protein, low molecular weight peptides of less than 3000Da, including black rice oligopeptides around 1300Da, were identified. These oligopeptides inhibited matrix metalloproteinase activity and stimulated hyaluronan synthase 2 gene expression in human keratinocytes in a dose-dependent manner, indicating potential to support extracellular matrix integrity and hydration. Three newly identified rice bran protein peptides with C-terminal tyrosine residues showed significant inhibitory effects against tyrosinase-mediated monophenolase reactions; one sequence, CT-2 (Leu-Gln-Pro-Ser-His-Tyr), potently inhibited melanogenesis in mouse melanoma cells without cytotoxicity, positioning rice bran protein as a potent source of tyrosinase-inhibitory peptides for melanin-related skin conditions [7].

In a separate cosmetic formulation, a biological peptide complex comprising di- and tri-peptides from rice and lupin proteins was optimized for rapid assimilation by skin cells and passage through the barrier; previous in vitro work showed that rice-derived di- and tri-peptides stimulate fibroblast proliferation and messenger RNA expression of procollagen, collagen VII and fibrillin-1, supporting dermal matrix rebuilding in anti-aging applications [11].

Silk fibroin peptide represents a marine-adjacent animal-derived ingredient obtained from the silkworm Bombyx mori. Experimental data demonstrate that silk fibroin peptide can inhibit inflammation and enhance the anti-inflammatory activity of tTAT-superoxide dismutase, which penetrates cells and tissues and exerts antioxidative activity in a mouse inflammation model. Despite these promising anti-inflammatory and antioxidant properties, no human in vivo efficacy data are currently available, emphasizing the need for translational studies before firm conclusions about cosmetic benefit can be drawn [7].

Keratin-based peptides illustrate animal-derived structural protein digestion applied directly in topical skincare. Formulations containing keratin-based peptides of molecular weight less than 1000Da have been described as hemostatic, moisturizing, repair-promoting and potentially radio-protective. In a placebo-controlled in vivo study with nine healthy females with dry skin types III to V, a 3% keratin-based peptide hand cream improved water-holding capacity, hydration and elasticity relative to deionized water and untreated areas, and appeared to prevent some damaging effects associated with surfactant exposure. Additional studies in six and 16 healthy females tested 3% keratin-based peptide in aqueous solution and internal wool lipid liposome suspension; both formulations improved skin barrier integrity and water-holding capacity, and combining keratin-based peptide with internal wool lipids led to further beneficial effects. These studies are limited by low participant numbers and lack of mechanistic detail, yet they support the concept that short keratin-derived peptides can enhance barrier function and hydration in dry, possibly aging skin [7].

Within daily moisturization strategies, sophisticated peptides and protein derivatives from wheat, rice, silk, soybean and oat are already used as humectant and film-forming agents. Quaternary N-alkyl derivatives of proteins or small polypeptides with long side chains increase lipophilicity, promote binding to the stratum corneum and improve percutaneous absorption, while

biomimetic small peptides that mimic collagen or enzyme sequences have been proposed as moisturizers with enhanced surface smoothing and hydration [2,5,7].

TABLE 3
SOURCES OF BIOACTIVE PEPTIDES FOR SKINCARE

Source	Examples	Key Activities	Evidence Level
Synthetic	Pal-KTTKS, Pal-GHK, Cu-GHK, Acetyl hexapeptide	ECM stimulation, neuro-modulation, copper delivery	Strong (clinical trials)
Bioengineered	Peptamide-6, Recombinant growth hormone	Collagen synthesis, growth factor stimulation	Moderate
Plant-Derived	Soybean peptides, Rice peptides, Lupin peptides	Collagen synthesis, MMP inhibition, tyrosinase inhibition	Moderate-Limited
Animal-Derived	Silk fibroin, Keratin peptides	Anti-inflammatory, barrier support, hydration	Limited

VI. FORMULATION SCIENCE OF PEPTIDE-BASED SKINCARE

Physicochemical constraints of peptides strongly influence their topical delivery and must be accounted for in formulation design. Successful transdermal molecules generally have molecular weight below 500Da, moderate lipophilicity with logP between 1 and 3, melting point below 200°C and reasonable aqueous solubility above 1 mg/mL. Diffusivity in the stratum corneum decreases with increasing size and number of hydrogen-bonding groups, and is maximal for small, non-hydrogen-bonding molecules. Peptides and proteins contain multiple amide bonds that act as hydrogen bond donors and acceptors, are often charged at physiological pH, and therefore intrinsically hydrophilic. These features drastically lower their diffusivity through the lipophilic stratum corneum, making this outer barrier the dominant obstacle for peptide penetration and necessitating delivery-enhancing strategies [9].

Several approaches exploit physicochemical modification and external energy to improve dermal access. Chemical penetration enhancers such as esters, fatty alcohols and fatty acids have been used to increase permeation of actives like melatonin across skin, although enhancement is dependent on enhancer structure and can be limited by local toxicity or irritation. Physical methods including electroporation, iontophoresis, sonophoresis and laser microporation can transiently disrupt barrier properties and have enabled delivery of large molecules such as insulin and cyclosporine A; however, these techniques require specialized equipment and their feasibility and reproducibility in routine cosmetic use remain challenging [9].

Conjugation of peptides to hydrophobic moieties such as fatty acids is another strategy to increase lipophilicity and stratum corneum partitioning. For example, a palmitoyl derivative of interferon α penetrated human skin 5- to 6-fold more efficiently than the unconjugated peptide, and topical palmitoyl KTTKS (palmitoyl pentapeptide-4) showed significantly greater clinical improvement in facial skin compared with the non-palmitoylated sequence. These data illustrate that tuning partition coefficient and charge through lipidation can markedly alter cutaneous bioavailability while preserving biological activity [9,12].

Nanotechnology-based carriers further address peptide stability and delivery requirements. Solid lipid nanoparticles are composed of physiological lipids and can encapsulate actives to protect them from enzymatic and chemical degradation, reduce transepidermal water loss, and provide controlled, sustained release that enhances therapeutic effect. Nonetheless, their relatively ordered solid matrices may limit drug loading and promote expulsion during storage. To reduce internal crystallinity and increase payload capacity, nano lipid crystal systems combine solid and liquid lipids, improving solubility of actives in the oil phase and minimizing expulsion. These particles share occlusive properties with solid lipid nanoparticles, forming films that enhance hydration and residence time on the skin surface. Importantly, several studies show that such lipid nanoparticles usually remain localized in the stratum corneum and appendages and do not readily cross into deeper epidermis, which restricts direct delivery to dermal targets unless additional permeation strategies are employed [12,13].

Cell penetrating peptides and related carriers provide complementary solutions by mediating translocation of nanocarriers and cargo across cellular membranes. Positively charged sequences rich in arginine and lysine, such as TAT, have been conjugated to solid lipid nanoparticles and liposomes to enhance deposition into deeper epidermal layers. In experimental systems, coating nanoparticles with TAT facilitated their movement from the stratum corneum into the viable epidermis, with depth profiling revealing fluorescence up to 120μm when occlusive film formation allowed progressive penetration. Mechanistically, early binding of the cationic peptide to the stratum corneum, water evaporation from the formulation, and occlusive lipid film formation precede CPP-guided movement into deeper layers. However, high cell-penetrating activity of some CPPs raises

safety concerns that drugs could be transported beyond intended layers into deeper tissues, underscoring the need to balance penetration enhancement with spatial control of distribution. Alternative CPPs with restricted exocytosis have been proposed to confine entry to epidermal cytosol while maintaining barrier integrity in reconstructed human epidermis models [12,14].

Peptide-containing creams and emulsions must also maintain molecular stability against environmental stress at the skin surface. Water-in-oil or oil-in-water formulations can create microenvironments that protect labile peptides, prolong residence time and slightly enhance transepidermal passage without disrupting barrier function. For tested CPP formulations, standard cosmetic vehicles provided sufficient stability and allowed penetration into epidermal layers while preserving cell viability, supporting their suitability for cosmeceutical applications [5,14].

Vehicles and dosage forms for peptide-based skincare must balance physical stability, controlled release and appropriate skin tolerability while maintaining peptide integrity. Emulsions are commonly employed, with oil and aqueous phases heated and combined under stirring to yield homogenous systems. An example is an argireline-containing lotion in which isopropyl myristate, glycerin monostearate, paraffin, cetyl alcohol, canola oil, non-ionic surfactants, humectants and preservatives are processed at 80°C before cooling and quality control testing. This formulation exhibited uniform white appearance, microscopic homogeneity of internal phases, a pH of 5.85±0.18 within the physiological skin range, and resistance to centrifugal stress and freeze–thaw cycling, indicating robustness against mechanical and thermal challenges typical of cosmetic storage and use conditions [15].

Dosage-form performance is further characterized by in vitro release and rheological behavior. For the argireline lotion, a 6-hour release study showed non-Fickian diffusion, interpreted as a combination of diffusion and erosion-controlled processes, with Higuchi kinetics providing the best fit (R^2=0.9949), consistent with diffusion-driven release from a semi-solid matrix. Rheological assessment reported a viscosity of 480rpm (instrument parameter), supporting suitable spreadability for topical application. Stability studies across different temperatures over 28 days revealed no changes in physical appearance, organoleptic properties or argireline content, and a skin irritation test in healthy volunteers showed no erythema or edema, underscoring the feasibility of such lotions as peptide delivery vehicles in routine skincare regimens [15].

Vehicle selection also interacts with peptide chemical stability. Work on acetyl hexapeptide-8 (Argireline) has shown that peptides can undergo substantial oxidation in complex cream or serum matrices, with oxidation often complete depending on formulation and sample handling. Accelerated stability testing demonstrated that Argireline content remained stable at 25°C but decreased to 59% and 41% after 24 hours at 40°C and 60°C, respectively. These observations highlight that process and storage temperatures are critical parameters in dosage-form design for bioactive peptides. Because methionine and other oxidation-prone residues can be converted to sulfoxides or sulfones during production, purification and storage, resulting in loss of function, reduced stability or increased aggregation, analytical characterization of peptide-containing vehicles is required to monitor side-chain modifications and ensure cosmeceutical potency over shelf life [16].

Beyond conventional emulsions, nanotechnology-based vehicles provide alternative dosage forms compatible with antioxidant and vitamin co-actives. Solid lipid nanoparticles encapsulate active ingredients within physiological lipids to protect against enzymatic degradation, prevent transepidermal water loss and deliver controlled, prolonged release, thereby enhancing therapeutic effect. Nano lipid crystal systems with mixed solid and liquid lipids further increase loading capacity and minimize drug expulsion during storage, while retaining occlusive film-forming properties on the skin surface. In cosmeceutical contexts these nanocarriers have been used for vitamins and antioxidants, such as liposomal sodium ascorbyl phosphate, to improve epidermal penetration and stability of otherwise labile molecules. Encapsulation can thus support compatibility between peptides and co-formulated antioxidants by shielding each component from degradative interactions and modulating their release profiles [5,12,17].

Nanoparticle-based dosage forms also have defined spatial distribution and penetration characteristics that bear on safety and compatibility. Studies with solid lipid nanoparticles and nano lipid crystals report that these particles generally do not cross the stratum corneum barrier; instead, they reside within this outer layer and release their cargo into the epidermis, aided by occlusive film formation that enhances hydration and residence time. When combined with cell-penetrating peptides such as TAT, lipid nanoparticles and liposomes can be guided into deeper epidermal layers, raising the possibility of co-delivering peptides with other actives like melatonin or cyclosporine. However, high translocation capability of some CPPs introduces a risk that actives might be transported beyond intended cutaneous targets, so compatibility assessments must consider not only chemical interactions between ingredients but also the depth and distribution of delivery achieved by the chosen vehicle and enhancer combination [12,14].

Compatibility with other topical anti-aging agents, notably retinoids and acids, depends on maintaining barrier function and minimizing irritation. Evidence on topical therapies shows that retinol, retinaldehyde, glycolic acid and azelaic acid improve epidermal turnover, dermal collagen, pigmentation and inflammation but can be irritative, particularly at higher concentrations or in sensitive skin. At the same time, humectant- and emollient-rich formulations containing glycerin or hyaluronic acid help preserve barrier integrity and hydration, enhancing tolerance to active ingredients. Incorporating peptides into vehicles that already contain humectants, emollients and barrier-restoring agents may therefore support their use alongside retinoids and acids, provided that pH, temperature and oxidative environment are controlled to protect peptide structure while maintaining the established efficacy and safety profiles of co-formulated actives [2,3,5,17].

TABLE 4
DELIVERY SYSTEMS FOR PEPTIDE-BASED SKINCARE

Delivery System	Mechanism	Advantages	Limitations
Chemical Penetration Enhancers	Disrupt lipid organization	Simple, cost-effective	Potential irritation
Lipidation (Palmitoylation)	Increase lipophilicity	Enhanced partitioning	Requires synthesis
Solid Lipid Nanoparticles	Encapsulation, occlusive film	Protection, controlled release	Limited loading capacity
Nano Lipid Crystals	Mixed solid/liquid lipids	Higher loading, reduced expulsion	Complex formulation
Cell-Penetrating Peptides (CPPs)	Transmembrane translocation	Enhanced epidermal penetration	Safety concerns
Emulsions (O/W, W/O)	Solubilization, skin hydration	Good tolerability, stable	Limited penetration

Source: Compiled from [5,9,12,13,14]

VII. EVALUATION OF PEPTIDE-CONTAINING SKINCARE PRODUCTS

Mechanistic assessment of peptide-based skincare relies heavily on in vitro and ex vivo models that recapitulate key features of adult and aging skin while allowing controlled manipulation of cellular pathways. Several studies have implemented culture systems of human dermal fibroblasts, keratinocytes, three-dimensional (3D) reconstructed skin equivalents and ex vivo biopsies to dissect peptide effects on collagen turnover, senescence, inflammation and barrier-related parameters [6,18,19].

For collagen-modulating peptides such as SA1-III (KP1), primary human dermal fibroblast cultures have been central. In one study, soluble collagen levels in culture media were quantified using an in-house sandwich enzyme-linked immunosorbent assay after SA1-III treatment, demonstrating increases comparable to positive controls L-ascorbic acid and transforming growth factor-β1. Follow-up mechanistic work combined Western blot analysis of type I collagen in cell lysates and conditioned media with gelatin zymography to profile matrix-degrading enzymes. These experiments showed that SA1-III elevates extracellular collagen predominantly by reducing degradation, with minimal influence on biosynthesis or fibroblast proliferation. Activity of MMP-2 and MMP-9 decreased in conditioned media, and gene expression of inflammatory mediators remained unchanged in resting and lipopolysaccharide-stimulated fibroblasts, indicating that collagen preservation occurred without pro-inflammatory signaling. Importantly, SA1-III was effective at reasonably low concentrations and across fibroblasts derived from donors spanning a wide age range, supporting its relevance for aging dermis [6].

Broader serpin A1-derived constructs have also been probed in vitro. Wound-healing models using monolayers of a kidney epithelial line and primary human skin fibroblasts showed that natural serpin A1, the synthetic C-terminal peptide A1-C26, and a serpin A1–insulin-like growth factor fusion protein all reduced wound size. A1-C26 significantly enhanced collagen I production in fibroblasts, whereas the chimera promoted fibroblast proliferation and thymidine incorporation. In primary keratinocytes, only the chimera reduced wound size, illustrating cell-type-specific responses and the utility of parallel fibroblast and keratinocyte assays to map peptide actions on repair processes [6].

Senotherapeutic evaluation of Pep 14 has used an integrated platform of human skin cells, 3D skin equivalents and ex vivo human skin biopsies. In multiple senescence-inducing models that mimic intrinsic chronological aging, Hutchinson–Gilford progeria syndrome (HGPS) and extrinsic stresses such as UVB and etoposide, Pep 14 treatment reduced cellular senescence and inflammation markers while enhancing cellular resilience and DNA repair. Single-cell RNA sequencing of HGPS fibroblasts revealed diverse subpopulations of senescent and non-senescent cells; pseudotime analysis showed that Pep 14 increased non-senescent and early-senescent cells and reduced late-senescent cells by supporting DNA repair and preventing

progression into advanced senescence. Across clusters, Pep 14 consistently lowered CDK2AP1 mRNA, leading to CDK2 activation and a transient cell cycle arrest that facilitates repair and limits accumulation of SASP-secreting late-senescent cells. Notably, apoptosis and autophagy-related mRNAs were not induced, indicating a senomorphic rather than senolytic mode of action [18,19].

Ex vivo human skin models have extended these mechanistic insights to tissue-level outcomes directly relevant to topical application. Treatment of ex vivo skin biopsies with Pep 14 formulated to deliver up to 2% of the peptide into the dermis led to improved histological scores, reduced mRNA expression of senescence markers such as p16, decreased IL-8 and TYR, and increased expression of keratins and collagen. A skin-specific DNA methylation clock (MolClock) was applied to quantify biological age; Pep 14 decreased methylation age by an average of 2.6 years, with similar reductions observed using other established clocks. In comparative ex vivo experiments, rapamycin reduced p16 and IL-8 expression but did not improve epidermal area or DNA methylation age, and in some parameters worsened tissue phenotype, highlighting that senescence marker reduction alone may not translate into global skin rejuvenation. Topical retinol, used as an anti-aging reference, induced stratum corneum peeling but increased CDKN2A and CXCL-8 mRNAs in both epidermis and dermis, changes plausibly associated with irritation and heightened senescence markers. These ex vivo data underscore the value of combined histologic, transcriptional and epigenetic readouts for mechanistic assessment of peptide formulations in human skin [1,18,19].

Collectively, fibroblast and keratinocyte monolayer assays, 3D skin equivalents and ex vivo biopsies provide complementary mechanistic information on peptide effects in collagen turnover, wound repair, senescence modulation and inflammation. Such models allow rigorous comparison of peptide candidates with established actives like retinoids and rapamycin under controlled conditions, and are essential for linking molecular pathways to functional rejuvenation markers before clinical evaluation [1,6,18,19].

Clinical and instrumental evaluation in human subjects is essential for determining whether peptide-containing formulations deliver meaningful anti-aging benefits beyond in vitro and ex vivo findings. Several trials have examined facial and periorbital wrinkles, hydration, elasticity and skin surface topography using standardized imaging and biophysical tools [7,11,20].

Palmitoyl pentapeptide pal-KTTKS has been evaluated in multiple placebo-controlled, double-blind human studies focused on periorbital wrinkles. In one trial, a 0.005% pal-KTTKS formulation applied twice daily for 28 days to the periocular region produced quantitative reductions in fold depth, fold thickness and skin rigidity by 18%, 37% and 21%, respectively, as measured by optical profilometry. These improvements were reproduced in two additional double-blind studies enrolling women with moderate to distinct periorbital wrinkles. A split-face, left–right randomized trial in 93 subjects further demonstrated significant enhancement in fine lines and wrinkles compared with vehicle, using wrinkle volume, wrinkle depth, skin roughness, elastin fiber density and collagen IV regulation at the dermal–epidermal junction as endpoints. These data illustrate how profilometry and histologically inferred matrix changes can be combined to substantiate clinical efficacy of signal peptides in vivo [7,9].

Clinical investigation of palmitoyl tripeptide-3/5 has similarly relied on instrumental wrinkle analysis. In vivo results with a cream containing 10–25ppm palmitoyl tripeptide-3/5 demonstrated dose-dependent wrinkle reduction quantified by PRIMOS surface topography. In an 84-day efficacy study with 60 Chinese volunteers, twice-daily application reduced skin roughness more effectively than control and placebo creams, and outperformed pal-KTTKS-containing formulations. These findings, based on objective surface profiling, support the concept that peptides which both stimulate collagen synthesis and interfere with MMP-1 and MMP-3 mediated collagen degradation can yield measurable improvements in wrinkle metrics in human subjects [7].

Cu-GHK has been the subject of several controlled trials examining dermal remodeling and global appearance. A non-randomized, four-arm active-controlled study compared creams containing GHK-Cu, tretinoin, vitamin C and melatonin applied to the thighs for one month. Immunohistological assessment of biopsies showed increased procollagen synthesis in 7/10 patients with GHK-Cu versus 4/10, 5/10 and 5/10 for tretinoin, vitamin C and melatonin, respectively. Additional studies over 8 and 12 weeks used visual evaluation and ultrasound to document improved skin laxity, clarity, fine lines, wrinkles, mottled hyperpigmentation, density and thickness, together with enhanced viscoelastic properties and keratinocyte proliferation, all without significant irritation. These trials integrate subjective scoring with quantitative imaging and histology to characterize the clinical performance of a carrier–signal peptide complex in photodamaged facial skin [7,9].

Other peptide-based formulations have been assessed with sophisticated instrumental approaches. A vitamin C serum containing rice-derived di- and tri-peptides, hyaluronic acid and mineralizing water was tested using Quantirides evaluation of

crow's-foot replicas and Toposurf 3D fringe projection analysis of wrinkle "peaks" and "valleys". After 29 days of use, the number, surface and length of crow's-foot wrinkles decreased, and topographic parameters indicated smoothing of the skin surface, findings that aligned with investigator clinical scoring and subject self-assessment of fine wrinkle improvement. Dansyl chloride labelling of the stratum corneum showed accelerated desquamation and epidermal renewal relative to untreated skin, supporting a rejuvenation effect at the tissue level, although the contribution of individual ingredients could not be disentangled. These methods exemplify how non-invasive optical and fluorescence techniques can capture changes in epidermal turnover and wrinkle morphology following peptide-containing treatments [11].

Formulation-focused clinical studies also provide information on safety and instrumentally measured performance. An argireline (acetyl hexapeptide-8) lotion formulated as an emulsion was assessed for stability and tolerability in human volunteers. Physical characterization showed homogenous appearance, appropriate pH and robust resistance to centrifugal and freeze–thaw stress. A 6-hour release study indicated non-Fickian diffusion governed by Higuchi kinetics, and skin irritation testing revealed no erythema or edema. Complementary work on argireline oxidation in creams and serums underscored that peptide content can decline markedly at elevated temperatures, highlighting the need to control storage conditions to maintain clinical efficacy. These observations link vehicle design, peptide stability and dermatological safety in the context of human use [15,16].

More broadly, clinical and instrumental approaches recommended for cosmeceutical evaluation include randomized controlled trials with defined inclusion and exclusion criteria, standardized measurements of hydration, elasticity, wrinkles and pigmentation, and use of non-invasive imaging such as dermoscopy and digital photography, alongside dermatological irritation and sensitization testing and appropriate statistical analysis. Such frameworks have been proposed to systematically assess peptide-based formulations within cosmeceutical practice [20].

TABLE 5
SUMMARY OF CLINICAL EVIDENCE FOR KEY PEPTIDE FORMULATIONS

Peptide	Study Design	Key Findings	Assessment Methods
Pal-KTTKS	Double-blind, placebo-controlled	18-37% reduction in fold depth, thickness, rigidity	Optical profilometry
Cu-GHK	Active-controlled (4-arm)	70% showed increased procollagen synthesis	Immunohistology, ultrasound
Palmitoyl tripeptide-3/5	84-day RCT (n=60)	Dose-dependent wrinkle reduction	PRIMOS surface topography
Vitamin C + Rice Peptides	29-day clinical study	Reduced crow's-foot wrinkles, smoother surface	Quantirides, Toposurf 3D
Acetyl hexapeptide-8	Stability and tolerability	No irritation, stable formulation	Skin irritation testing

VIII. SAFETY, REGULATORY AND ETHICAL CONSIDERATIONS

Dermatological safety of peptide-containing skincare must be considered in the broader context of cutaneous responses to topical agents, particularly in adult and aging populations with fragile skin and frequent polypharmacy. Elderly individuals exhibit increased susceptibility to adverse reactions because of chronic use of topical and systemic medications, cumulative environmental exposures and structural skin changes that compromise barrier integrity. Stronger medications are recommended only when the expected therapeutic benefit justifies the associated risk, underscoring the need for cautious selection and monitoring of any bioactive ingredient used on aged skin [21].

Contact dermatitis represents a key safety concern. Allergy-type reactions remain common among older adults despite an age-related reduction in delayed-type hypersensitivity responses, which arises from decreased numbers of Langerhans cells, diminished T-cell populations and reduced vascular reactivity. These immunological changes would be expected to lower individual susceptibility to allergic contact sensitivity, yet decades of potential sensitization and increased exposure to topical preparations sustain a significant burden of allergy in geriatric patients. Topical medications are identified as the most frequent culprits, with reports that up to 81% of patients treated for chronic leg ulcers exhibit allergic reactions to these agents. In this context, patch testing prior to the introduction of new topical medications is advocated for high-risk groups, such as those with dermatitis or ulceration of the lower extremities, with test panels including medicaments, dressings, dental prostheses and ocular medications. Generalized allergic rashes in the aged are far more often attributed to medicines than to food, and agents may additionally provoke phototoxic or photoallergic responses by increasing sensitivity to sunlight [21].

Against this background, available data on cosmetic peptides are relatively reassuring but remain incomplete. A survey of proteins and peptides used in cosmetics notes that some proteins are linked to skin allergy, including contact dermatitis, yet no evidence was found that peptides currently employed in cosmetic formulations raise specific safety concerns of this type. Furthermore, protein hydrolysates that contain bioactive peptides are categorized as Generally Recognized as Safe by the FDA, providing a regulatory indication of acceptable systemic and dermatologic risk under normal conditions of use. Nonetheless, this evaluation emphasizes the diversity of peptide structures and acknowledges that many cosmetic trials assess formulations containing peptides together with multiple other active ingredients, making it difficult to clearly attribute observed benefits or adverse effects to peptides alone. These limitations highlight the need for well-controlled safety assessments that isolate peptide contributions to cutaneous responses, particularly in vulnerable aging skin [4,14].

Immunological and inflammatory aspects are also central to peptide safety. Some bioactive peptides derived from food proteins show anti-inflammatory and immunomodulatory properties in systemic models. For example, pea protein hydrolysate significantly reduces lipopolysaccharide/interferon-γ-induced nitric oxide production and suppresses TNF-α and IL-6 in macrophages, while maintaining cell viability, and enhances phagocytic activity and beneficial cytokine profiles in mice. Fermented milk-derived peptides similarly decrease proinflammatory TNF-α and IL-6 and increase IL-10 in tumor models, suggesting anti-inflammatory and potential anticancer activities. Although these findings are based on oral administration and systemic outcomes, they illustrate that peptides can interact with immune pathways in ways that may theoretically influence cutaneous inflammation, underscoring the importance of characterizing immunological effects when adapting such molecules or related sequences for topical use in adult and aging skin [22].

Methodological frameworks for cosmeceutical evaluation provide practical guidance for structuring safety investigations. Recommended approaches include dermatological assessments of irritation and sensitization, systematic monitoring of adverse reactions and side effects, and adherence to ethical and regulatory requirements. Clinical trial designs call for clear inclusion and exclusion criteria, standardized measurement of parameters such as hydration, elasticity, wrinkles and pigmentation, and use of non-invasive imaging modalities to complement subjective questionnaires. Safety assessment protocols emphasize the need to document severity and frequency of cutaneous events and to interpret data within the context of existing scientific evidence on active ingredients, including peptides. These structured methods are particularly relevant for peptide-based formulations intended for aging populations, where immunological shifts, comorbidities and concurrent medications may modify both risk and benefit profiles [20].

Regulatory framing of peptide-containing products determines how they can be marketed, what evidence is required, and which claims are permissible. Cosmeceuticals are defined as topical products, typically creams, lotions, serums and ointments, that are designed to improve the appearance of aging skin but are generally not tested or approved as drugs that alter cellular functions. Their presence on the market is often justified by theoretical benefits derived from in vitro studies of active ingredients rather than by formal drug-level clinical evaluation. Regulations governing concentration of components and the scope of activity claims differ across countries and organizations, which creates heterogeneous standards for peptide-based formulations and complicates cross-jurisdictional comparison of products [16].

Within this framework, peptides are one category of active ingredients among retinoids, antioxidants and growth factors that are incorporated into cosmeceuticals to target specific skin concerns such as aging, hyperpigmentation and acne. Methodological guidance for evaluation of such products stresses that active ingredients and formulations should be linked to clearly defined skin conditions and mechanistic targets, and that scientific evidence must support claims of efficacy and safety. Recommended procedures include comprehensive literature review, identification of key actives, in vitro and in vivo experimentation, randomized controlled trials, and structured safety assessment, all conducted under ethical and regulatory oversight. These steps are intended to align peptide-containing cosmeceuticals with standards that bridge cosmetics and pharmaceuticals, even though formal drug approval pathways may not be pursued [20].

Labeling practices for cosmetic peptides operate within ingredient nomenclature systems and claim restrictions. In Europe, a dedicated glossary of common ingredient names for cosmetic labeling lists hundreds of entries containing the word "peptide," reflecting the diversity of sequences used in anti-aging products. Anti-aging cosmetics are selected for analysis when labels contain terms such as anti-wrinkle, anti-aging, wrinkle repair, regenerator, aging, anti-slackening or firming, indicating that peptide-related claims are typically framed around improvement of appearance rather than treatment of disease. Exploratory analysis of multinational anti-aging products emphasizes that claims of "anti-wrinkle" or "firming" are tied to the presence of signal peptides, carrier peptides, neurotransmitter-inhibiting peptides or enzyme-inhibiting peptides, but also notes that many formulations combine peptides with other actives, complicating attribution of labeled benefits to specific molecules [4,7].

Safety-related aspects of regulatory status intersect with labeling in several ways. Protein hydrolysates containing bioactive peptides are categorized by the FDA as Generally Recognized as Safe, which provides a baseline regulatory acceptance for their use in cosmetic contexts. At the same time, surveys of cosmetic peptides report that, although some proteins are linked to contact dermatitis, no evidence has been found that peptides used in cosmetics raise specific allergy concerns. These observations support current practice in which peptide-containing products are labeled and marketed without special allergen warnings beyond standard cosmetic requirements, but they also underscore that safety data often derive from heterogeneous sources and that individual peptide contributions are rarely isolated in clinical trials [4,7].

Claims regarding penetration, activity and "cosmeceutical" status increasingly involve nanotechnology-based vehicles and cell-penetrating peptides. Research on nanoemulsions, nanoparticles and peptide-enhanced creams shows improved penetration of vitamins, antioxidants and biofunctional peptides, and these findings are cited in support of claims about enhanced delivery and bioavailability in labeled products. However, such studies frequently acknowledge that clinical trials using formulations with multiple actives do not clearly differentiate peptide effects from those of other ingredients. Methodology papers therefore call for standardized clinical trial designs, clear inclusion and exclusion criteria, objective endpoints such as hydration, elasticity, wrinkles and pigmentation, and detailed safety monitoring to substantiate marketing claims for peptide cosmeceuticals within regulatory constraints [12,14,20].

TABLE 6
SAFETY CONSIDERATIONS FOR PEPTIDE-BASED SKINCARE

Consideration	Key Points	Recommendations
Contact Dermatitis	Potential for sensitization in aging skin	Patch testing in high-risk groups
Irritation	Generally well-tolerated	Monitor for erythema, edema
Photoallergy	Limited evidence	Sun protection advised
Immunological Effects	Theoretical immune modulation	Characterize immunological effects
Regulatory Status	GRAS for hydrolysates	Follow local regulations
Polypharmacy	Interactions with other topicals	Cautious introduction

IX. PRACTICAL INTEGRATION OF PEPTIDE FORMULATIONS INTO SKINCARE ROUTINES

Designing peptide-inclusive skincare regimens for adult and aging skin requires coordinated attention to cleansing, treatment layering, moisturization and photoprotection, together with appropriate clinical evaluation of outcomes. Structured protocols for integrating cosmeceuticals begin with gentle cleansing tailored to skin type, followed by targeted treatment steps using serums, and completion with moisturizers and broad-spectrum sunscreens. Cleansers remove dirt, oil and makeup, toners can help rebalance pH, and treatment serums deliver active ingredients such as peptides to address concerns including fine lines, hyperpigmentation and acne. Moisturizers then hydrate and seal in water, while sunscreens protect against ultraviolet damage and premature aging, with reapplication during sun exposure to preserve benefits from cosmeceutical actives [2,20].

Adult and aging skin often exhibits increased dryness, barrier fragility and cumulative photo-damage, making daily barrier care central to regimen design. Regular use of moisturizers containing humectants such as glycerin, hyaluronic acid, urea, lactic acid and amino acid derivatives, together with occlusives like petrolatum, mineral oil and lanolin, improves water-holding capacity of the stratum corneum and reduces transepidermal water loss. More sophisticated peptides and proteins, including lipophilic quaternary N-alkyl derivatives of proteins or small polypeptides, are already used as moisturizers to bind the horny layer and enhance percutaneous absorption. Biomimetic small peptides that mimic collagen or enzyme sequences have been proposed for surface smoothing and hydration, and protein derivatives from wheat, rice, silk, soybean and oat contribute humectant and film-forming properties that are particularly useful in dry, photoaged skin. Selecting oil-in-water or water-in-oil formulations according to dryness severity further adapts regimens to skin profiles, with richer creams preferred for marked xerosis [2].

Integration of peptide-based treatments into these routines benefits from methodologically robust assessment frameworks. Recommended protocols call for in vitro studies of cell proliferation, collagen synthesis and antioxidant activity, followed by in vivo trials in human volunteers to measure hydration, elasticity, wrinkles and pigmentation using standardized techniques. Subsequent randomized controlled trials should employ clear inclusion and exclusion criteria, cover diverse age groups, skin types and ethnicities, and combine subjective questionnaires with objective imaging such as dermoscopy and digital photography. Dermatological safety assessments, including irritation and sensitization tests with systematic monitoring of adverse reactions, are essential when regimens for aging skin incorporate potent actives like peptides alongside retinoids, acids

or antioxidants. Statistical analysis comparing treatment and control arms allows clinicians and pharmacists to interpret regimen performance and refine product combinations for specific adult and elderly profiles [20].

Day-to-day implementation for aging skin emphasizes sequencing and layering that maximize penetration while limiting irritation. Evidence indicates that cosmeceuticals achieve better efficacy when applied to clean, dry skin, starting with the thinnest products, such as toners or serums, and gradually moving to thicker creams or ointments, allowing each layer to absorb before the next is added. Consistency and patience are highlighted; sustained use over weeks to months is necessary before measurable improvements in skin texture, wrinkles and elasticity become apparent. Sunscreen use every morning, with reapplication, protects against UV-driven oxidative stress that would otherwise undermine peptide-induced collagen synthesis and barrier repair. These practical rules are supported by research on penetration enhancement, photoprotection and long-term outcomes of topical antiaging strategies [3,20].

Adult and aging skin regimens that incorporate peptides must also account for broader therapeutic choices. Topical retinoids such as retinol and retinaldehyde, glycolic acid and azelaic acid possess strong evidence for improving epidermal renewal, dermal collagen and pigmentation, but are associated with irritation risks, especially in sensitive or older phototypes. Combining these actives with humectant- and emollient-rich bases helps maintain barrier integrity, and regimented introduction (for example, alternating nights or lower initial concentrations) can be guided by clinical monitoring of tolerability. Concurrent use of peptide-containing products within such regimens should be evaluated through well-designed trials that document changes in wrinkles, hydration and pigmentation, while safety assessments track sensitization or irritant reactions and support ethical, evidence-based optimization of peptide-centric routines for varied adult and aging skin profiles [2,3,20].

Integration of peptide-containing skincare with office-based dermatologic procedures requires understanding how professional interventions remodel skin structure and signaling, creating windows in which topical actives may exert enhanced or altered effects. Energy-based devices such as intense pulsed light (IPL) use non-coherent, broad-spectrum light filtered between 500 and 1200nm to target melanin and hemoglobin, treating dyschromia, telangiectasias, lentigines and texture irregularities via selective photothermolysis. IPL stimulates dermal fibroblasts, increases collagen synthesis through sublethal thermal injury and activation of transforming growth factor-β signaling, and yields improved elasticity, reduced fine lines and smoother skin tone, typically after three to six sessions spaced at 3–4 week intervals with maintenance every 6–12 months. Side effects are generally mild, but pigmentary risk is higher in Fitzpatrick IV–VI phototypes, where strict photoprotection and cautious parameter selection are essential. These fibroblast-stimulating and collagen-inducing effects suggest that peptide formulations designed to support extracellular matrix homeostasis could be logically positioned in post-IPL regimens that already rely on barrier-restoring humectants, emollients and ceramide-containing products to maintain hydration and protect against transepidermal water loss [3].

Laser resurfacing approaches, including fractional ablative CO_2 and non-ablative modalities, induce wound repair responses with collagen remodeling and elastin synthesis. Ablative lasers vaporize epidermal and dermal structures by targeting water as chromophore, achieving robust correction of moderate-to-severe photoaging at the cost of longer recovery and higher risks of post-inflammatory hyperpigmentation and infection. Fractional ablative CO_2 lasers create microscopic zones of ablation surrounded by intact tissue and are regarded as a gold standard for balancing efficacy and safety; expert consensus emphasizes individualized parameters and structured post-procedural skincare to mitigate complications. Non-ablative lasers such as Nd:YAG, Er:Glass and diode systems act via dermal coagulation without epidermal disruption, offering reduced downtime but requiring more sessions. Meta-analyses show comparable overall wrinkle reduction and patient satisfaction between ablative and non-ablative lasers, with ablative systems trending toward superior improvement in severe photoaging [3].

In this context, layering peptide-containing formulations after laser resurfacing should account for altered barrier integrity, heightened inflammatory signaling and the concurrent use of agents like retinoids or niacinamide that modulate collagen, elastin and immune pathways [3]

Mechanical rejuvenation techniques also create opportunities for synergistic use of topical peptides. Microdermabrasion removes the stratum corneum using abrasive crystals or diamond-tipped devices and vacuum, inducing increased cell turnover, fibroblast activation and neocollagenesis with improvements in smoothness, tone and radiance, while remaining limited to superficial photoaging and mild dyschromia. Microneedling generates controlled microinjuries with dermarollers or motorized pens, upregulating collagen types I and III and extracellular matrix remodeling, effectively improving texture, fine wrinkles and scars such as atrophic acne scars. Emerging microneedle patch technologies employ dissolvable or hydrogel arrays that deliver antioxidants, extracellular vesicles, mRNA or stem-cell-derived products directly into the dermis to combat photoaging at a molecular level. Preclinical work with patches loaded with adipose-derived extracellular vesicles demonstrates collagen

remodeling, reduced oxidative stress and enhanced epidermal structure, positioning microneedle-based delivery as a promising platform for transdermal administration of peptides, proteins and other biomolecules. Broader microneedle arrays fabricated from biocompatible polysaccharides like hyaluronic acid, chondroitin sulfate, alginate and chitosan can create reversible microchannels, bypass stratum corneum resistance, and enable sustained release profiles with low toxicity, supporting their use for cosmetic indications including aging, wrinkles and depigmentation [3,13].

When peptide-based products are combined with such mechanical or microneedle procedures, regimen planning must consider timing relative to injury and repair phases, penetration depth, and the potential for enhanced bioavailability that might amplify both desired matrix effects and any irritation or sensitization risks already recognized for actives like glycolic and azelaic acids, retinoids and niacinamide [3].

Injectable and minimally invasive procedures further shape the milieu in which topical peptides act. Botulinum toxin type A selectively inhibits acetylcholine release at the neuromuscular junction, softening dynamic wrinkles in glabellar lines, forehead creases and crow's feet. Hyaluronic acid fillers restore volume and re-establish youthful facial proportions, with some formulations also stimulating neocollagenesis. Biostimulatory approaches such as calcium hydroxylapatite fillers and absorbable polydioxanone or poly-lactic acid sutures promote collagen I and III production, tissue contracture and improved vasculature in animal and tissue culture models, with benefits that may decline or persist depending on thread type and time course. Platelet-rich plasma delivers concentrated growth factors including TGF-β, PDGF, FGF and IGF, with modest but documented benefit for aging skin, especially as an adjuvant to laser resurfacing. These professional interventions alter extracellular matrix composition, fibroblast signaling and vascular architecture; topical peptide regimens introduced alongside or following them should be structured using evidence-based methodologies that integrate objective measures of wrinkles, elasticity and pigmentation, standardized inclusion criteria and safety monitoring, as proposed for cosmeceutical trials [3,20].

X. CONCLUSION

This synthesis highlights how short bioactive peptides interact with key cutaneous compartments to modify extracellular matrix turnover, cell signaling and repair pathways. Signal and carrier sequences such as palmitoyl-conjugated collagen fragments, Cu-GHK and decorin-mimetic tripeptides have demonstrable effects on collagen, elastin and glycosaminoglycan dynamics, while modulators like SA1-III can reduce proteolytic collagen loss by attenuating MMP activity. Senotherapeutic sequences exemplified by Pep 14 influence PP2A/AKT and FoxO-related networks to reduce late-stage senescence markers and support DNA repair without triggering apoptosis, producing favorable ex vivo tissue responses including increased epidermal thickness and reduced methylation age metrics.

Delivery constraints imposed by the stratum corneum demand physicochemical modification, lipidation, nanoparticulate encapsulation or transient barrier disruption for deeper dermal targeting; each approach alters spatial distribution and bioavailability and therefore must be matched to the intended molecular target and safety profile. Translational pathways benefit from a staged evaluation framework that integrates molecular, cellular and tissue models with rigorous clinical and instrumental endpoints. In vitro and ex vivo assays clarify mechanism of action and off-target signals, three-dimensional skin equivalents connect cellular responses to organ-level outcomes, and randomized human trials with profilometry, ultrasound and biochemical readouts validate functional benefits such as wrinkle depth reduction, elasticity improvement and increased procollagen synthesis.

Safety assessment should prioritize irritation, sensitization and potential photoallergic effects in older, barrier-compromised cohorts, and regulatory labeling must reflect the level of evidence supporting claims. Future work should refine delivery systems to balance epidermal versus dermal exposure, expand controlled comparative trials that isolate peptide effects within complex formulations, and apply standardized endpoints including epigenetic clocks and objective imaging to establish durable, reproducible benefits for adult and aging skin.

CONFLICT OF INTEREST

The author declare no conflict of interest.

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