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REVIEW

Hydrolyzed Marine Collagen: Emerging Evidence of Benefits via the Oral Route – Review and Insights for Medical Aesthetics Practitioners

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Video Abstract

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Introduction and Purpose: Marine collagens are environmentally friendly and biologically compatible collagens derived from aquatic organisms, including invertebrates like sponges and jellyfish. Starting from marine collagens as raw materials, sophisticated purification procedures lead to low-molecular-weight, bioactive fragments that are valuable functional ingredients for nutritional supplements, cosmeceuticals, and medical devices in regenerative medicine. From the mid-2010s to the late 2010s, several high-quality studies highlighted the skin bioregenerative properties of marine collagen-derived oligopeptides. The purpose of this review is to discuss these properties and their rationale.

Methods: This review only analyzes studies focused on skin regeneration published in indexed journals with significant impact factors (the rule was rigid for human studies), supplemented by a few contributions from Google Scholar for methodologically sound in vitro and animal studies.

Results: Activation of skin fibroblasts with high systemic bioavailability after oral intake supports the bioregenerative properties of hydrolyzed marine collagen. Marine collagen hydrolysates do not cause irritation or inflammation and have a negligible impact on pro-inflammatory mediators in animal studies. Preclinical research indicates that 50 µg/mL of hydrolyzed marine collagen peptides accelerates cell migration almost as effectively as 10 µg/mL of recombinant human epidermal growth factor, although the predictive value of in vitro studies for humans remains uncertain. Accelerated wound healing with collagen neosynthesis is associated with increased expression in immunohistochemistry of platelet-endothelial cell adhesion molecule-1, basic fibroblast growth factor, and transforming growth factor ß-1. Furthermore, enzyme-treated hydrolysates produced under acidic conditions exhibit antioxidant effects without affecting pro-inflammatory cytokines, while enzyme-treated hydrolysates under alkaline conditions have the opposite effect.

Conclusion: An increasing number of preclinical and human studies highlight the skin and overall bioregenerative properties of hydrolyzed marine collagens. Their high systemic intestinal absorption after oral intake distinguishes them from hydrolysates from other sources. Long-term safety should be a primary concern of future research.

Keywords: biological waste management, collagen hydrolysates, collagen peptides, fibroblast activation, hydrolyzed marine collagen, skin regeneration

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Introduction

Three polypeptide α-helices, each composed of 1014 amino acids and weighing about 100 kDa, twist around each other in a triple superhelix stabilized by hydrogen bonds. They form a superfamily of trimeric molecules that are essential for helping the skin and subdermal tissues to withstand the mechanical stresses and maintain tissue architecture.[1–3] Collagens, the name for these trimeric molecules, are crucial for specialists in aesthetic medicine, skin regeneration, and aesthetic plastic surgery. Nevertheless, those specialists are often unaware of their critical role in their daily practice.

Collagens, measuring approximately 280–300 nanometers (nm) in length and 1.4 nm in diameter, are the most abundantly produced proteins in humans and all vertebrates, making up about 30% of the body's total protein content. Type I is the dominant form in the extracellular matrix of the human skin dermis and subdermal tissues, accounting for up to 80% in young skin, with a decline of approximately 1.5% per year with age; Type III mainly accounts for residual non-type I collagen.[1–3] Five molecules of the highly evolutionarily conserved type I collagen spontaneously pack in parallel into quasi-hexagonal, right-handedly twisted fibrils, exhibiting a staggering D-period of about 67 nm (the D-banding seen in electron microscopy), and are about 500 micrometers (μm) long and 500 nm in diameter (Figure 1).[3,4]

Aesthetic and regenerative medicine and surgery have seen the approval of many collagen-based minimally invasive injectable derivatives worldwide.[3] The natural filling effect and ease of degradation by matrix metalloproteinases, cathepsins, and neutrophil elastase, along with the high homology in Type I collagen amino acid makeup among vertebrates—up to 95%—explain their success in regenerative medicine and tissue engineering.[3] Newly synthesized collagen scaffolds gradually replace injected collagen-based implants. Between 1981 and the US introduction in 2003 (in the early 1990s in some European countries) of the first injectable fillers for cosmetic use—based on hyaluronic acid and allergy-free but short-lived human-derived collagen (actually sourced from cadavers)—the first bovine collagen fillers, derived from cowhide, required two allergy tests before treatment, frequent injections, and rarely lasted more than three months, remaining the only FDA-approved injectable at that time.[3]

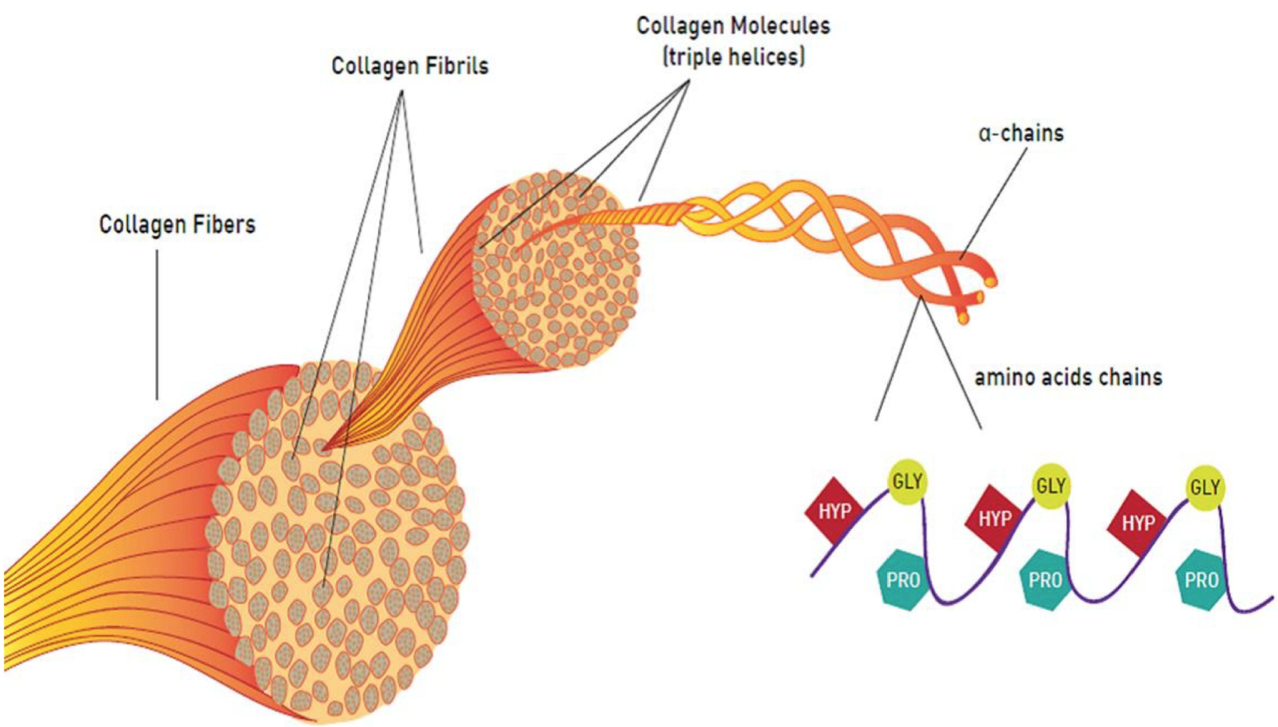


Figure 1 Structure of collagen fibers and fibrils showing evidence of the repeating units glycine-proline-hydroxyproline (GLY-PRO-HYP), which are characteristic of all collagens regardless of source. The high glycine content, around 30% (lower in some sponge species), helps stabilize the α-helix and the overall triple-helix structure of collagen. Reproduced from Sibilla S et al under the terms of a Creative Commons CC BY-NC 4.0 License.[4]

Native Marine Collagen and Hydrolyzed Marine Collagen

The latest technological developments in collagen derivatives originate from organisms such as seawater and freshwater fish, jellyfish, echinoderms, sponges, and other water invertebrates. They are collectively called marine collagens.[5–7] This review aims to present and discuss the limited high-quality evidence available regarding the biological properties of these collagen peptide fragments, the rationale behind these properties, safety and allergic issues, the risk of contamination, and their potential influence in aesthetic medicine.

Marine collagens, predominantly Type-I and metabolically compatible, may offer advantages over collagens from land vertebrates. They are an abundant resource that addresses religious concerns and avoids the risk of transmitting zoonotic prion diseases, such as bovine spongiform encephalopathy. Furthermore, collagens from land vertebrates are richer in arginine and are more likely to be beneficial as supplements to alleviate joint pain, improve flexibility, and enhance mobility.[5–8] Marine collagens are also environmentally friendly because they convert the voluminous and polluting waste products from the marine processing industry into sophisticated, high-yield, and low-cost raw materials for high-added-value products.[9,10] Fish skins, fins, heads, guts, scales, and bones make up 70% to 85% of the total catch weight; the estimated waste from these by-products exceeds 20 million tonnes annually.[5–8] The purification technology of these collagen fragments reduces to irrelevance the risk of contamination from marine pollutants, with special reference to highly toxic heavy metal contamination accumulating in marine alimentary chains.[5–8] Even Type I, II, and III collagen fragments sourced from marine organisms that filtrate enormous volumes of seawater and are thus at risk of concentrating pollutants such as jellyfish *(Acromitus hardenbergi)*, were free of heavy metal contamination, and in vitro toxicity was nil.[8]

Without cross-linking treatment, native collagen from fish, which is naturally less cross-linked than collagen from land vertebrates, is unsuitable for tissue engineering due to poor mechanical strength. However, highly absorbent and abundantly available native marine collagen may have other applications: for instance, as drug-impregnated membranes for the local delivery of antibiotics and antiseptics as it undergoes resorption, as artificial clot-like devices that hold many times their weight in blood for bleeding control, and to facilitate wound healing thanks to glycosaminoglycan content.[5,7]

A series of in vitro studies was groundbreaking, enabling the industrial production of chemical and enzymatic hydrolysis processes to convert marine collagen peptides into valuable functional ingredients for hydrolyzed marine collagen-based cosmeceuticals and medical devices with applications in regenerative medicine.[4,5] Initial steps include size reduction and removal of non-collagenous proteins, pigments, and fats using sodium hydroxide, alcohols, hydrogen peroxide, and ethylenediaminetetraacetic acid (EDTA) for demineralization. Sequential acidic and/or enzymatic treatments enable the extraction and denaturation of collagen into single-strand filaments, thereby disrupting the triple-helix spatial organization. Salt precipitation and enzymatic hydrolysis, followed by sequential ultrafiltration and chromatographic techniques, ultimately release the bioactive, marine collagen-derived small peptides (Figure 2).[4,5]

Methods

Due to their high systemic bioavailability after oral intake, as discussed in the following chapters, hydrolyzed marine collagens are widely distributed throughout the body, including the joints, with effects on other mesenchymal cells such as chondrocytes and synoviocytes similar to those on dermal and subcutaneous fibroblasts. Several studies discuss their potential usefulness in these areas, but these studies are beyond the scope of this review, which focuses on skin benefits.[4] The authors aimed to help aesthetic medicine specialists assess the value of these relatively new collagen derivatives for their everyday clinical practice. Therefore, they decided to limit their review to high-level preclinical and human studies, published in indexed peer-reviewed journals with significant impact factors, and focusing on the biological properties of these collagen derivatives in the skin.

A PubMed search conducted by the author M.R. in early June 2025, using the search string "hydrolyzed marine collagen" and restricted to English-language articles, yielded only 70 citations. The number of citations had not increased in a renewed PubMed search in early November 2015. Most of these were research papers and reviews primarily focused on technological issues. Several citations addressed topics unrelated to skin, such as joints. A prerequisite for reviewing in vitro and animal studies—indexed in PubMed and occasionally Google Scholar or cited in indexed reviews focused on

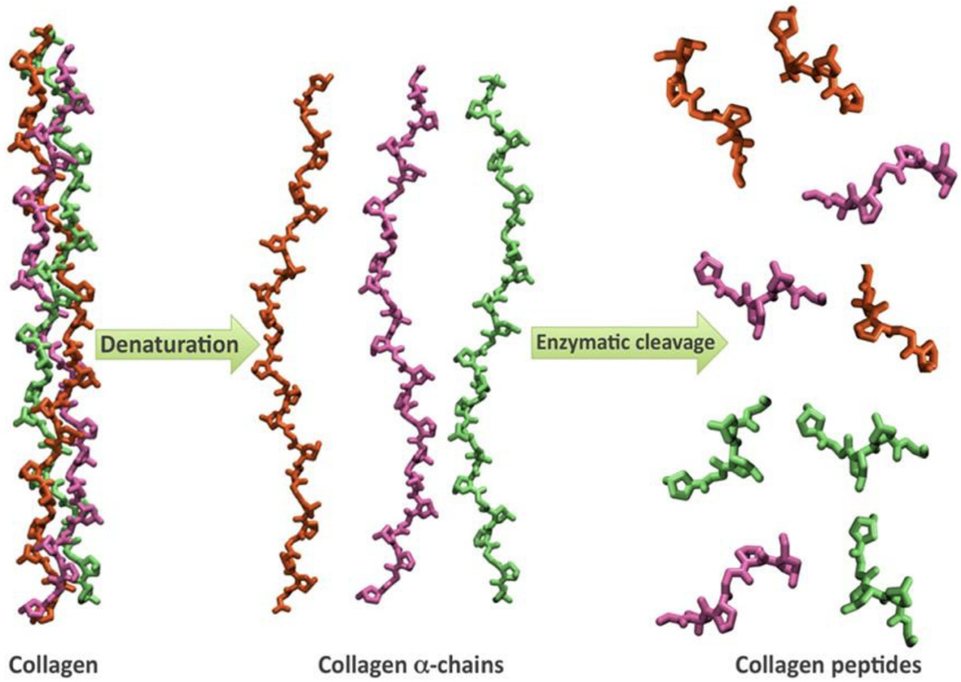


Figure 2 Sequential chemical and enzymatic hydrolysis steps that produce marine collagen fragments. Reproduced from Sibilla S et al under the terms of a Creative Commons CC BY-NC 4.0 License.[4]

technological and pharmaceutical issues—was that all procedures had to be well-documented and the studies reproducible without technical difficulties.

More stringently, the authors chose to limit the review of human clinical studies to the most recent, methodologically sound, and those published in PubMed-indexed journals with notable impact factors. They excluded all human studies of questionable quality— such as those with unclear inclusion and exclusion criteria, purely subjective efficacy endpoints, and rudimentary statistics—if published in non-indexed journals or cited in reviews primarily focused on technological issues. As of April 2025, only about thirty such studies are available. The mid-2010s marked the time when the first papers on hydrolyzed marine collagens appeared in the literature, and that period was set as the search cutoff in the consulted databases.

The authors made the final decision about which non-human and human studies to include in the review during an online consensus meeting held at the end of April. They put significant effort into reviewing the limited high-level literature that passed their strict selection process, adhering as closely as possible to the formal PRISMA guidelines.[11] However, they also maintained a general narrative style to make reading easier.

Results

Hydrolyzed Marine Collagens Exhibit Peculiar Biological Properties

In one of the earliest pilot investigations, enzyme-linked immunosorbent assays (ELISA) using fish collagen hydrolysates for inflammatory mediators such as interleukin (IL)-6 and IL-18 showed no irritative or inflammatory effects and revealed intriguing and potentially beneficial bioactivities.[4]

This study was the first in an expanding body of research exploring the somewhat unexpected biological properties of marine collagen fragments. The available literature, particularly in indexed, peer-reviewed journals with high impact factors, remains comparatively limited, mostly preclinical, and heavily focused on technological issues.

That early finding was not entirely unexpected. The oligopeptides, released by matrix zinc-dependent metalloproteinases during extracellular matrix collagen breakdown in both normal and disease conditions, are collectively known as matrikines if they can bind to cell surface receptors of chemokines, cytokines, ion channels, and growth factors, acting as messenger molecules in both health and disease.[12,13] Binding occurs through specific domains near the protease cleavage sites.[13] Several recognized matrikines, due to their high homology to marine collagen fragments, are good models to elucidate the effects of marine collagen hydrolysates. Examples include the tripeptide N-acetyl-Pro-Gly-Pro (PGP), a strong chemoattractant for neutrophils during inflammation; the collagen oligopeptide α1 C-1158/59, which improves wound healing and cell migration; and the C-propeptide fragment, an endothelial chemoattractant, all originating from the breakdown of Type-1 collagen.[12–16] Additionally, the glycine- and proline-containing PGP strongly inhibits keratinocyte proliferation and migration. The glycine residues help stabilize α-chains through hydrogen bonds, while proline and hydroxyproline are essential for their tight, left-handed twisting and interactions with fibroblasts and other matrix cells.[12] The effects of the PGP tripeptide depend on the chemokine receptors C-X-C motif chemokine receptor 1 (CXCR1) and CXCR2. In other words, under normal homeostatic conditions, the continuous and spontaneous turnover of collagen regulates both the inflammatory and epithelialization phases of wound healing, thereby supporting skin homeostasis.[12,15,16] Several recent papers have reviewed the skin regenerative effects of collagen breakdown oligopeptides.[12–14,17]

In two other preclinical examples from studies conducted in the mid-to-late 2010s, collagen hydrolysates derived from codfish skin promoted the viability of human fibroblasts. They also acted as powerful antioxidants, scavenging free radicals more efficiently than hyaluronic acid. Furthermore, exposure to collagen fragments from salmon skin showed unexpected neuroprotective activities by increasing the expression levels of phosphorylated cAMP-response element binding protein (p-CREB) and brain-derived neurotrophic factor (BDNF).[18,19] Two additional preclinical studies conducted in the 2010s demonstrated that exposure to marine collagen peptides accelerated wound closure in a dose-dependent manner after twelve hours. In the in-vitro scratch assay (Figure 3), the cell migration speeds were similar between 50 µg/mL of marine collagen peptides and 10 µg/mL of recombinant human epidermal growth factor (rhEGF) in positive controls.[20] Likewise, in animal models following cesarean section, peptides derived from hydrolyzed chum salmon skin collagen promoted wound healing with increased collagen production (Figure 4) and significantly enhanced immunohistochemical expression of platelet-endothelial cell adhesion molecule-1 (PECAM-1, CD31), basic fibroblast growth factor (bFGF), and transforming growth factor ß-1 (TGF-β1).[21]

The distribution of fragments in hydrolyzed marine collagen preparations from various marine sources is remarkably consistent, with only minor differences in amino acid composition and steady homology with bovine and porcine collagen. A marker of low antigenic potential and the risk of type-1 immediate hypersensitivity is the low content of histidine, the precursor of histamine.[22]

However, collagen hydrolysates exhibit different biological properties depending on the manufacturing methods.[22] Single enzyme-treated hydrolysates produced under acidic conditions mostly display antioxidant effects without significantly reducing pro-inflammatory cytokines. In contrast, single enzyme-treated hydrolysates obtained under alkaline conditions exhibit opposite properties.[23] The hydrolysates generated by using two proteases sequentially, such as the codfish preparation mainly favored by the authors (Nashira COLLAGEN, Astéria Pharma, Milan, Italy), have both antioxidant and anti-inflammatory effects.

Due to their low molecular weight, marine collagen oligopeptides are highly soluble in water. They are widely distributed throughout the body, significantly affecting skin hydration and elasticity. For example, in laboratory models supplemented with oral marine collagen hydrolysate for 24 months, histological, immunohistochemical, and Western blot analyses of chronologically aged skin revealed a dose-dependent reduction in collagen loss and fragmentation, along with notable increases in the expression of Type I and III collagen compared to aged untreated controls.[24] This evidence correlated with decreased metalloproteinase-1 (MMP-1) expression and elevated tissue levels of the MMP-1 inhibitor, linked to activation of the SMAD signaling pathway and up-regulated expression of the SMAD activator TGF-βRII (TβRII), again suggesting a direct effect on fibroblasts (SMAD: related proteins that are the primary signal transducers for receptors of the TGF-ß or Transforming Growth Factor beta superfamily).[24] The heightened endogenous collagen production reflects a general boost in fibroblast vitality, as demonstrated by the dose-dependent rise in fibroblast proliferation following extended exposure to marine collagen peptides (Figure 5).[25]

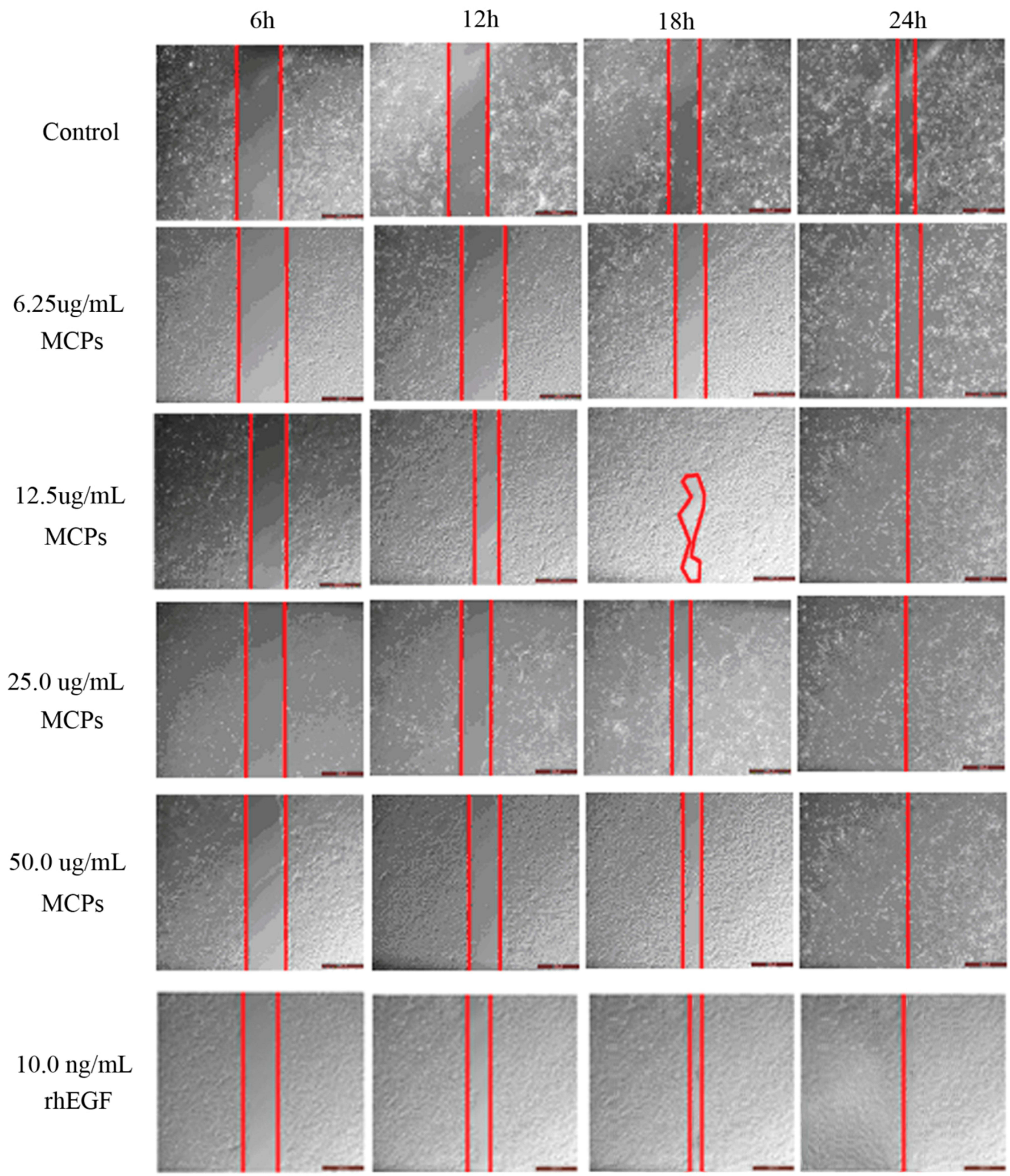


Figure 3 Dose-dependent effects of marine collagen fragment concentrations, ranging from 6.25 to 50 μg/mL, in an in vitro scratch closure assay; scale bar: 100 μm, MCPs: marine collagen proteolysates, rhEGF: human recombinant Epidermal Growth Factor. Reproduced from Hu Z et al under the terms of a Creative Commons CC BY-NC 4.0 License.[20]

The hydrolyzed marine peptides activate the intracellular NF-κB p65 signaling pathway in fibroblasts in a dose-dependent manner, which then triggers several other signaling pathways and the expression of growth factors (Figure 6).[25]

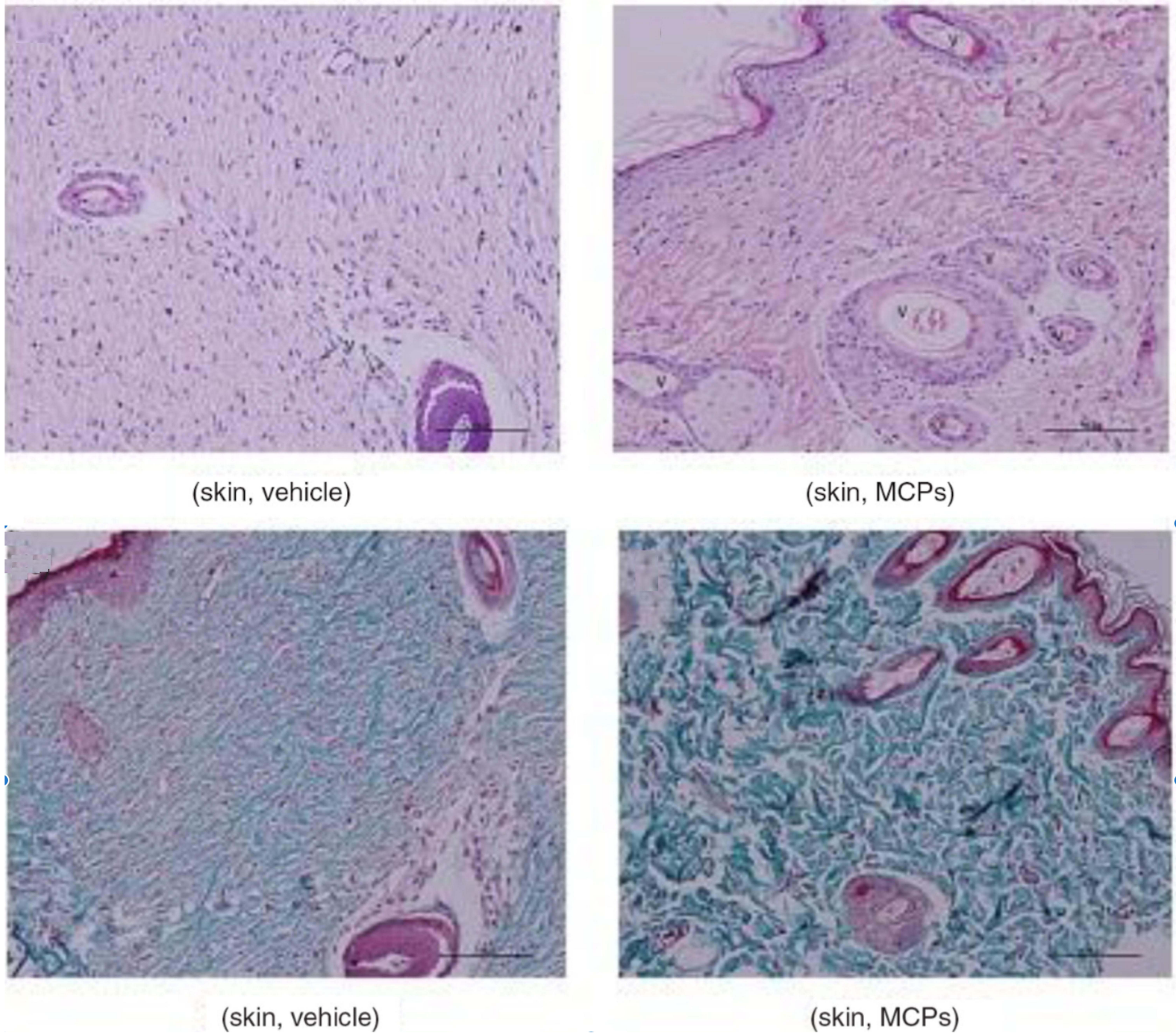


Figure 4 Noticeable collagen buildup in skin wounds of lab rats treated with an inert vehicle and 1.125 mg/g of hydrolyzed marine collagen peptides after 7 days (top micrographs) and 21 days (bottom micrographs); MCPs: marine collagen proteolysates Staining: hematoxylin and eosin for the top images; Masson's trichrome for the bottom images; 5 μm sections magnified at 5×40 and reproduced from Wang J et al under the terms of a Creative Commons CC BY-NC 4.0 License.[21]

Likely Benefits for Connective Tissue Regeneration from High Systemic Bioavailability

The low molecular weight of marine collagen fragments offsets the low thermal stability of native marine collagen compared to bovine collagen, due to fewer proline and hydroxyproline residues.[26]

Orally ingested native collagen or its partially hydrolyzed form, gelatin, is not absorbed efficiently, with only about 40% of digested collagen or gelatin slowly reaching the systemic circulation after intestinal breakdown.[27,28] Conversely, the systemic bioavailability of collagen's low-molecular-weight, ^{14}C-labeled fragments is higher and faster because it is mediated by transporters in the intestinal brush-border membrane, such as the proton-coupled oligopeptide transporter 1 (PepT1), and is therefore independent of digestion. The systemic bioavailability is similar to that of the amino acid proline (about 60% reaching the blood after the first-pass effect by enterocytes and hepatocytes).[29,30]

All hydrolyzed collagens are absorbed efficiently; however, the smaller fragments of low molecular weight from marine collagens have an advantage in terms of high solubility and systemic bioavailability, as well as more rapid bloodstream circulation. Absorption of hydrolyzed marine collagens is up to 1.5 times more efficient than that of collagen fragments from land mammals, probably due to the higher glycine, serine, and threonine content and lower levels of

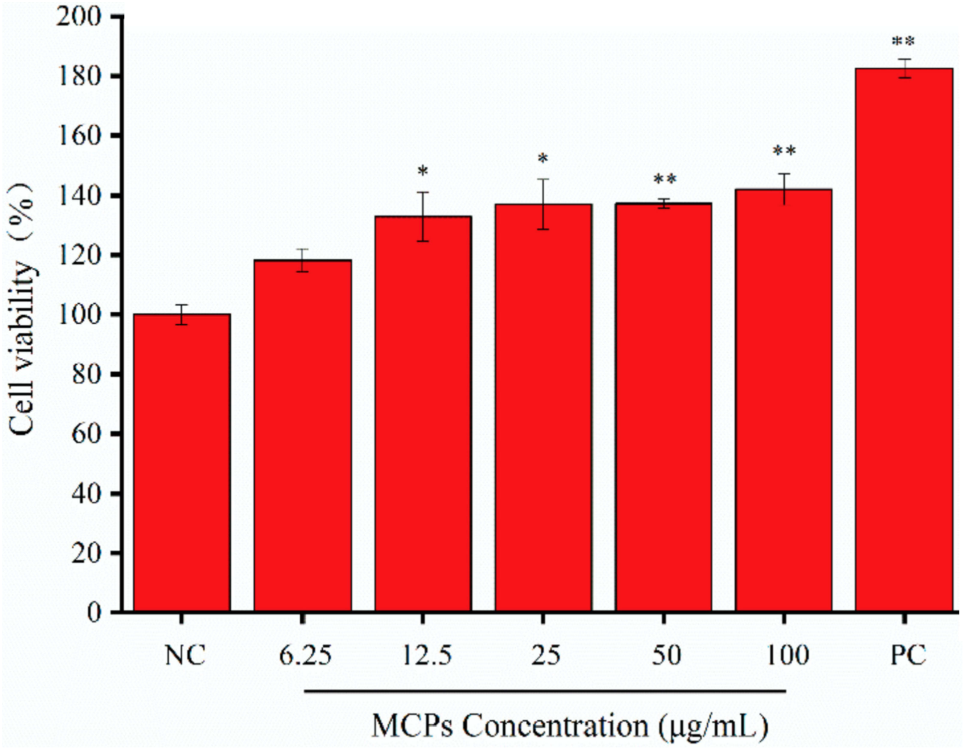


Figure 5 Dose-dependent fibroblast proliferation in vitro after 72 hours of exposure to hydrolyzed marine collagen peptides (MCPs) derived from *Nibea japonica* skin. PC: positive control (DMEM 10%), NC: negative control (DMEM 0.4%). DMEM: Dulbecco's Modified Eagle Medium. *p <0.05 and **p <0.001 compared to negative controls. Reproduced from Yang F et al under the terms of a Creative Commons CC BY-NC 4.0 License.[25]

proline and hydroxyproline compared to mammalian collagens.[8,31] Radioactivity remains in the skin for over two weeks (Figure 7), indicating that, once hydrolyzed collagen oligopeptides reach the dermal target for skin regeneration, they exert their dermal effects steadily and persistently.[4,32]

Summarizing the key findings of non-human investigations on hydrolyzed human collagen, demonstrated through some methodologically sound examples, the consistent outcomes of experimental studies, and insights into the possible molecular mechanisms behind these favorable results, these studies provide a solid overall rationale for exploring the potential of marine collagen hydrolysates in aesthetic applications through well-designed, demonstrative human studies.

Evidence of Regeneration in Human Studies Began in the Mid-to-Late 2010s

Due to the recent introduction of hydrolyzed marine collagens in medical aesthetics, the number of published papers indexed in PubMed is limited, and sometimes, those that do exist do not explicitly target specialists in this field. In 2018, a randomized, placebo-controlled study on dietary supplementation with collagen peptides and the amino acid ornithine showed an increase in skin elasticity and a decrease in pore count (Figure 8).[33] In their final comments, even in those early years, the authors noted that

> Compared with collagen peptide derived from land animals, collagen peptide derived from these aquatic sources has unique molecular and biological properties for amino acid composition, antioxidant activity, neuroprotective activity, and anti-skin aging activity, because of low temperature and/or high salt condition in the surrounding environment.[33]

The tripeptide glycine-X-Y, where X and Y are two amino acids, along with the dipeptides proline-hydroxyproline and hydroxyproline-glycine, appears especially crucial for bioactivity, possibly with variations in the amino acid composition contributing to the "unique molecular and biological properties of collagen peptide derived from aquatic sources".[33] Regarding safety, the authors observed neither adverse events, including adverse events related to the ingestion of hydrolysates, nor severe changes in biochemical or hematological parameters.[33] Three years earlier,

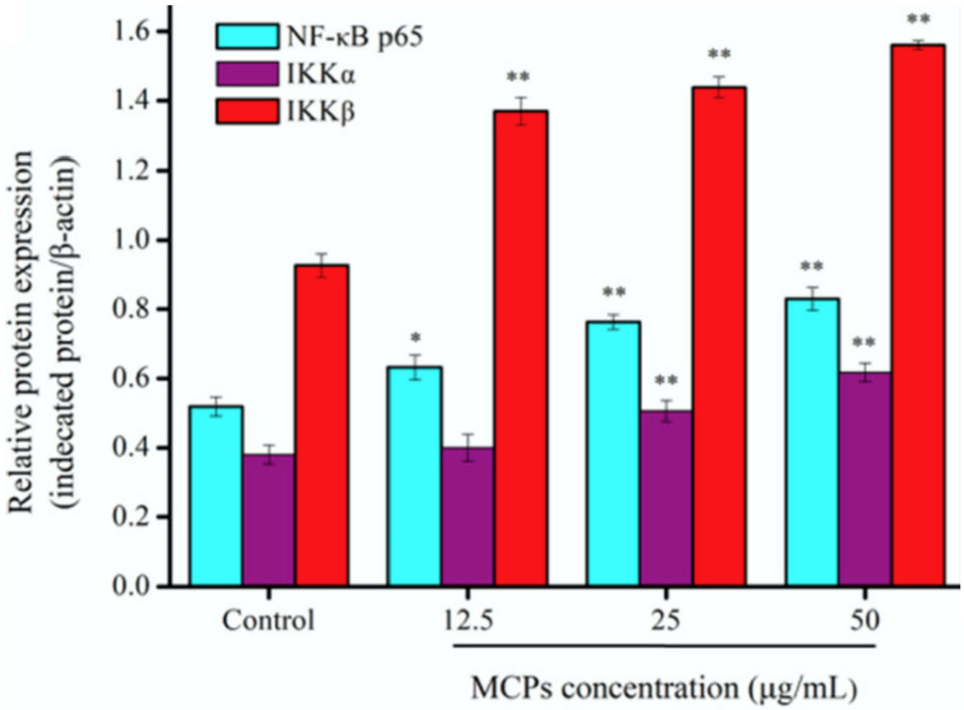


Figure 6 Expression levels of the primary signaling pathway NF-κB p65 and the secondary, dependent signaling pathways IKKα and IKKβ; Western blot analysis conducted after 72 hours of exposure to hydrolyzed marine collagen peptides (MCPs) from *Nibea japonica* skin compared to non-exposed controls. Means ± standard deviation; **p* <0.05 and ***p* <0.001 compared to controls. Reproduced from Yang F et al under the terms of a Creative Commons CC BY-NC 4.0 License.[25]

a pioneering placebo-controlled clinical trial examined whether daily oral supplementation with marine collagen peptides affected skin hydration (measured by corneometry), collagen density (evaluated using high-resolution ultrasound), and collagen fragmentation (measured by reflectance confocal microscopy). The study showed a nine percent increase in collagen density in the dermis and a dose-dependent increase in dermal collagen in human skin explants of up to five percent, "an important biological increase in light of the high basal amount of collagen in the papillary dermis."[34] The authors noted that collagen neosynthesis, which leads to increased echogenicity, might favorably influence skin wrinkling because reduced dermal echogenicity and increased skin wrinkling are interconnected.[34,35]

Another randomized, double-blind, placebo-controlled study conducted in Korea in 2018 showed that collagen hydrolysate purified from sutchi catfish skin, which contained at least 15% glycine tripeptide and included 3% glycine-proline-hydroxyproline, quickly improved skin hydration after six weeks (already 7.23 times higher compared to the placebo) and provided sustained benefits over the subsequent weeks and months. The collagen hydrolysate also favorably impacted skin elasticity and crow's feet wrinkling, even at the low dose of 1,000 mg per day (Figure 9).[36]

In recent years, the results of double-blind, placebo-controlled clinical trials using quantitative and unbiased techniques, such as high-resolution ultrasound and reflectance confocal microscopy imaging, have provided valuable, objective insights into the dermal rejuvenating effects of hydrolyzed marine collagens, which are especially relevant to everyday office practice. Here are just two examples of recent methodologically sound trials.[37,38]

In 2020, another carefully designed triple-blind trial examined the effects of a twelve-week intake of high-dose hydrolyzed marine collagen sourced from the tropical freshwater fish *Pangasius hypophthalmus* in middle-aged women, who exhibited visible facial signs of both chronological aging and photoaging. The trial observed a significant reduction in nasolabial wrinkles after three months of oral collagen supplementation, as measured by the VISIA skin analysis system (+35% compared to baseline).[37] Over twelve weeks, skin elasticity improved by 23% compared to the placebo group (maltodextrin powder), with hydration rising by 14%, radiance by 22%, and skin firmness by 25%, based on self-reported skin quality visual analogue scores. Results were particularly positive in women aged 45–54 years.[37]

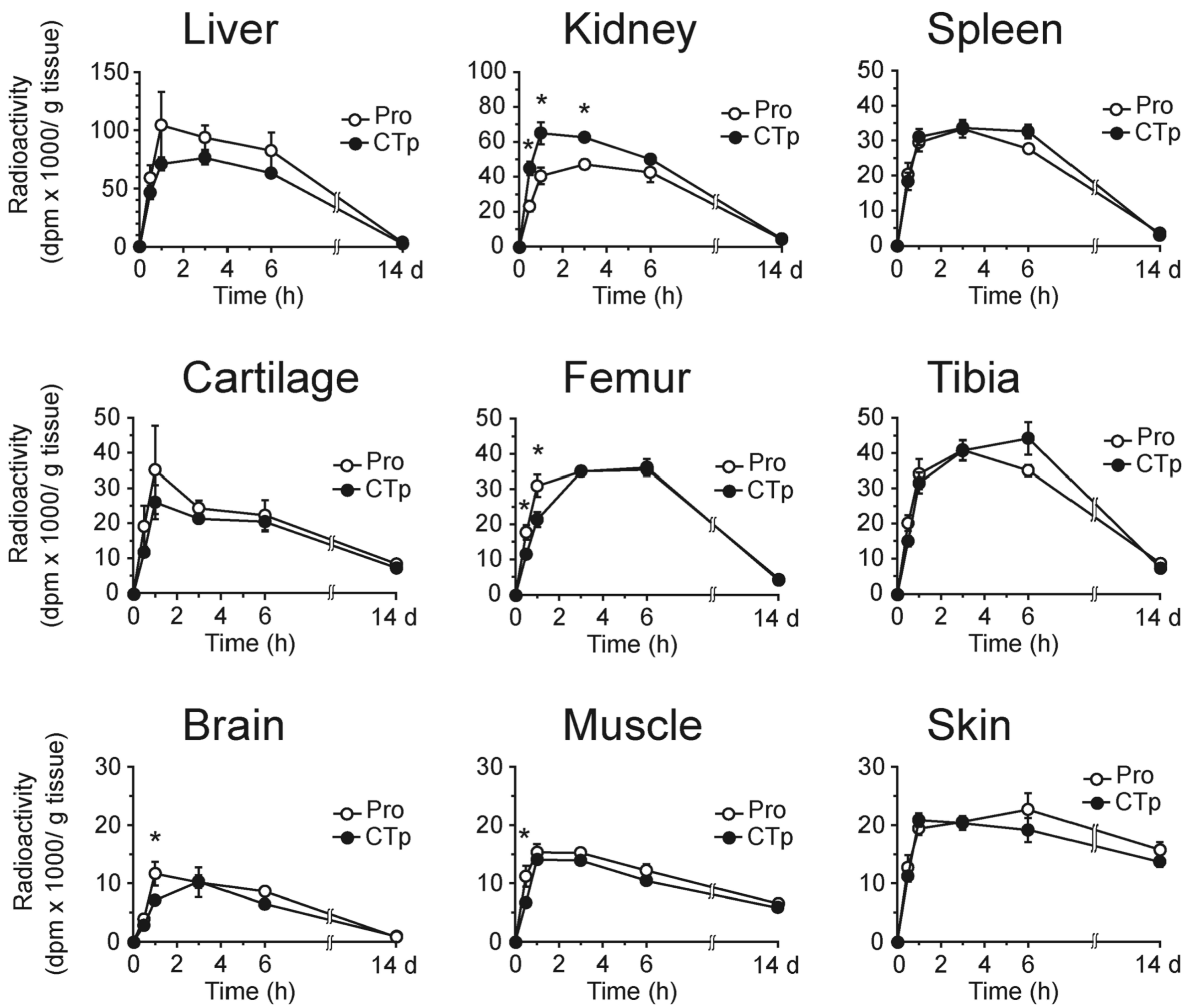


Figure 7 Distribution of radioactivity throughout the system, normalized to 1 g of wet tissue, in laboratory Wistar rats at 0.5, 1, 3, 6 hours, and 14 days after administering[15] C-labeled hydrolyzed collagen fragments (CTp) and proline (Pro); mean ± standard error. Reproduced from Sibilla S et al under a Creative Commons CC BY-NC 4.0 License.[4]

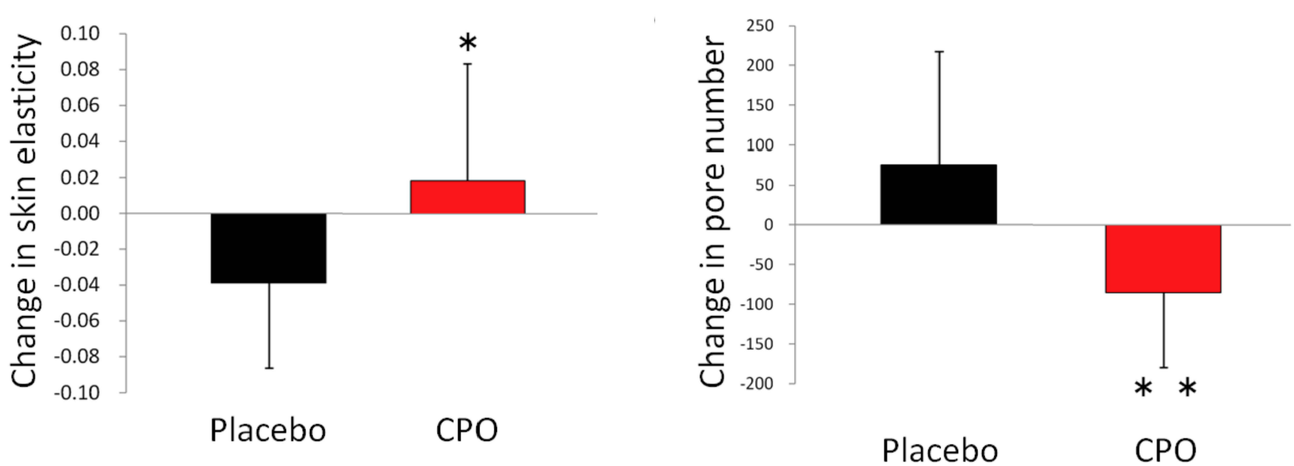


Figure 8 Changes in skin elasticity (left graph) and the number of pores (right graph) compared to baseline; *p <0.05 and **p <0.01 vs baseline. CPO: Collagen peptides and ornithine. Reproduced from Ito N et al under the terms of a Creative Commons CC BY-NC 4.0 License.[33]

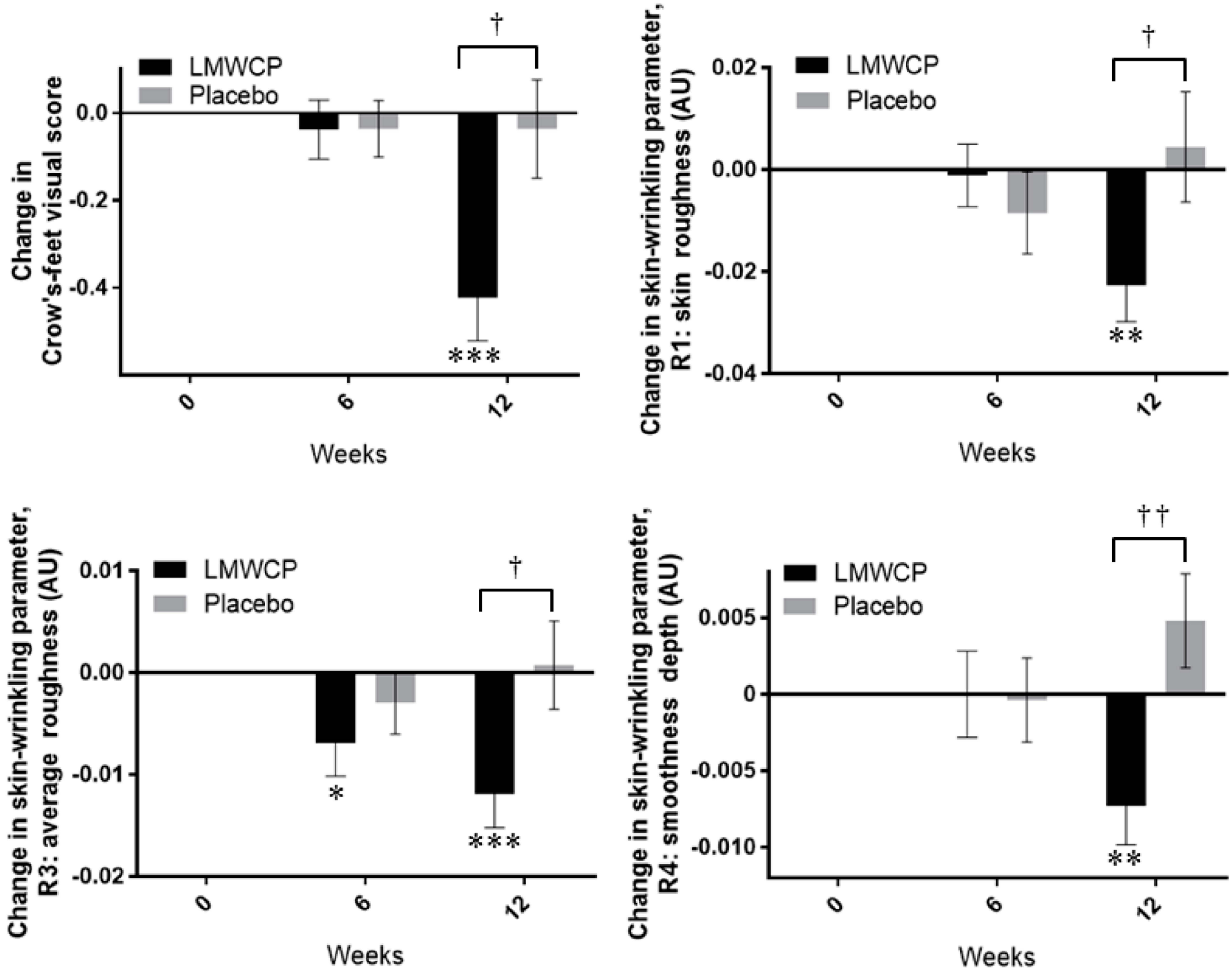


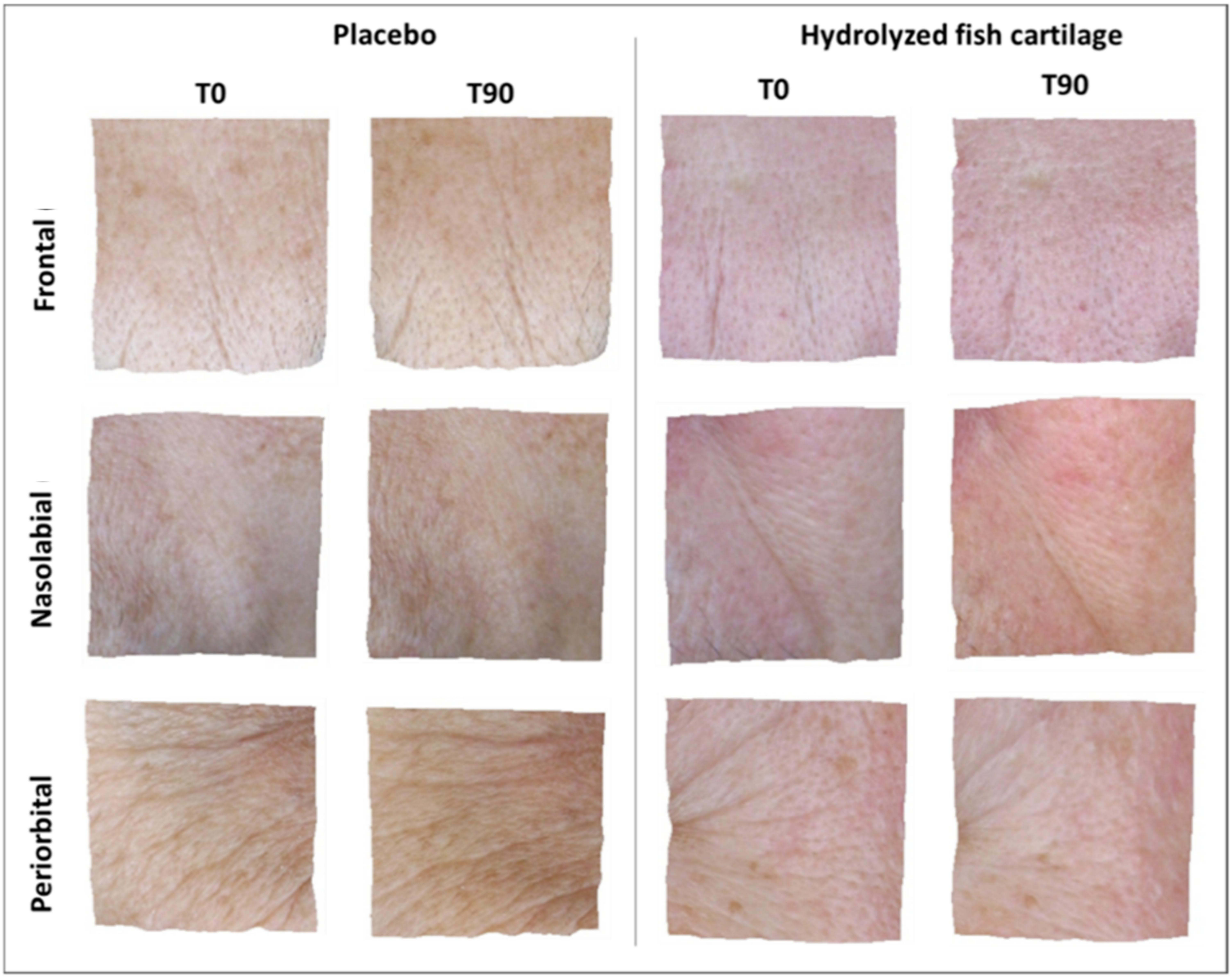
Figure 9 Changes in visually assessed Crow's feet scores (top left) and skin-wrinkling parameters, including skin roughness (top right), average roughness (bottom left), and smoothness depth (bottom right), measured with a Skin Visiometer SV600 in arbitrary units (AU), compared to baseline and placebo. Data are shown as mean ± SEM. **p* <0.05, ***p* <0.01, ****p* <0.001 versus baseline; † *p* <0.05, †† *p* <0.01 versus placebo. Reproduced from Kim D-U et al under the terms of a Creative Commons CC BY-NC 4.0 License.[36]

More recently, in a 2023 double-blind, placebo-controlled clinical trial, a ninety-day oral intake of hydrolyzed marine collagen from fish cartilage was associated with noticeable and significant reductions in wrinkles in the frontal and nasolabial areas, as well as the periorbital skin (–14±0.68%, –31±0.81%, and –26±0.66%, respectively, compared to baseline values; (Figure 10). The improved appearance of wrinkles was linked with enhancements in dermis echogenicity, while reflectance confocal microscopy image analysis showed improved collagen morphology (reduced huddled collagen and increased coarse collagen) and decreased elastosis (Figure 11).[38]

The lack of clinically significant adverse events was notable in all reviewed human studies with hydrolyzed marine collagen, with a safety profile of the various preparations similar to that of the placebo, and only occasional cases of mild nausea.[34–39]

Discussion

The decreased collagen density and dermal thickness are signs of skin aging, along with reduced synthesis and replacement of structural proteins essential for maintaining the skin's barrier function, such as filaggrin.[37] With a primary impact on the dermis, the decline in collagen, collagen fibril density, and fibroblast size leads to increased wrinkling, sagging, laxity, and a textured appearance.[7]



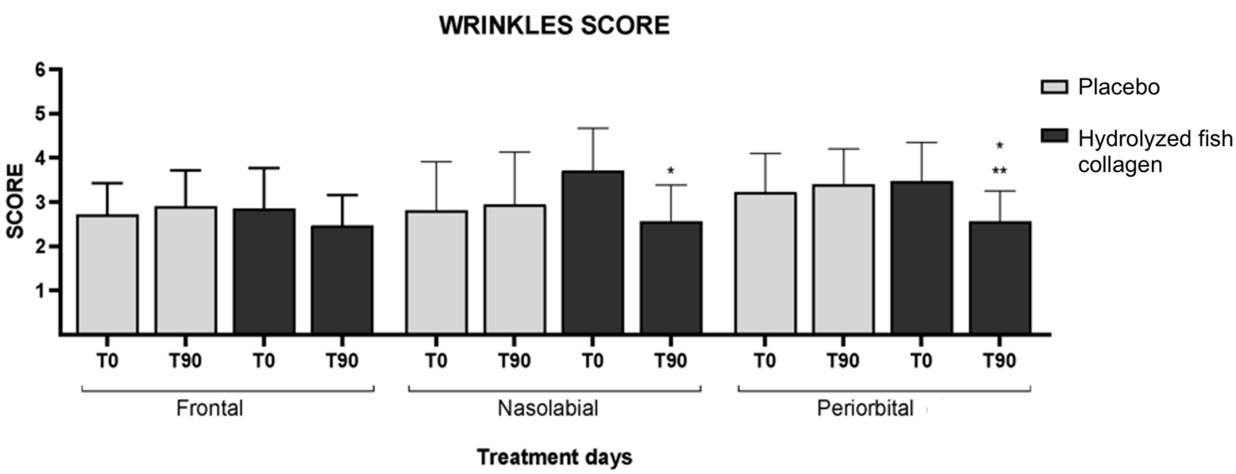


Figure 10 Microphotographs in the upper box: three-dimensional high-resolution images of facial wrinkles in the frontal, nasolabial, and periorbital areas before (T0) and after 90 days (T90) of supplementation with hydrolyzed fish cartilage or placebo. The lower graph displays quantitative analysis using Visioface® Quick software version 1.0.3.4 (**p* <0.05 compared to baseline, ***p* <0.01 compared to placebo). Reproduced from Maia Campos PMBG et al under the terms of a Creative Commons CC BY-NC 4.0 License.[38]

Due to their amino acid composition, the "green" collagens from marine waste resources inherently have less tensile strength than collagens derived from land mammals. However, the oligopeptides purified through thermal and chemical denaturation, along with enzymatic hydrolysis, demonstrate high systemic bioavailability, similar to that of proline.[4] This

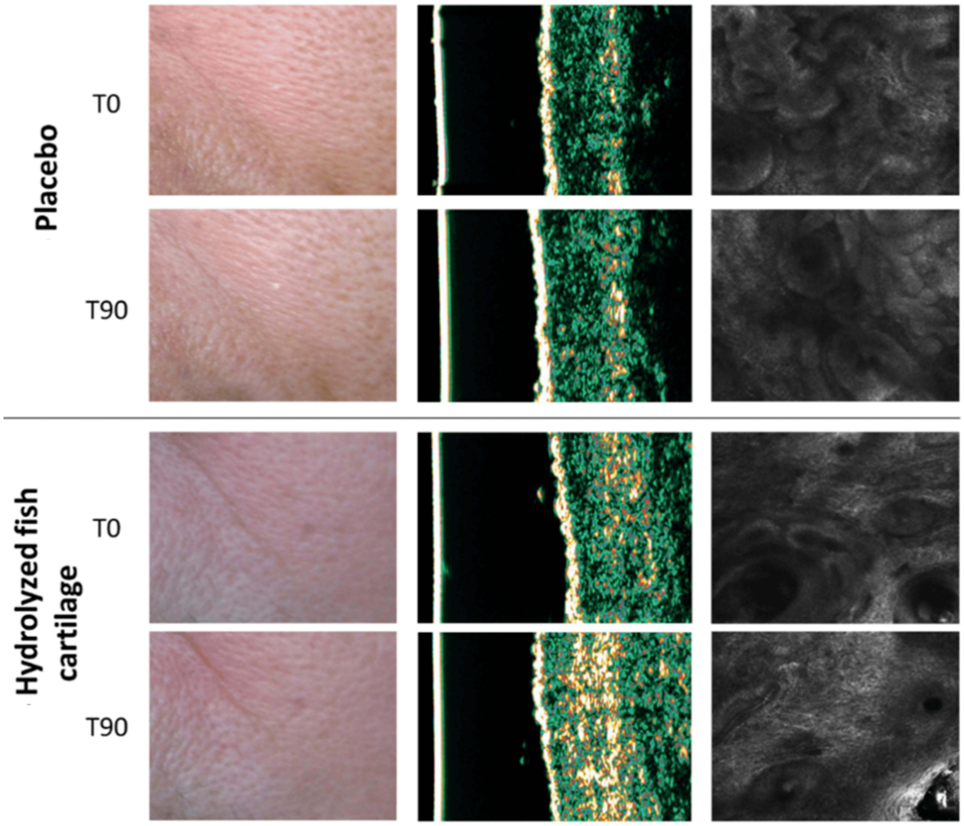


Figure 11 Representative images of skin showing wrinkle reduction (the four high-resolution microphotographs on the left), increased dermis ultrasound echogenicity (the four middle microphotographs), and better structure of collagen morphology assessed with reflectance confocal microscopy s(the four microphotographs on the right) after 90 days of supplementation with hydrolyzed marine collagen from fish cartilage (T90) compared to baseline (T0) and placebo. Reproduced from Maia Campos PMBG et al under the terms of a Creative Commons CC BY-NC 4.0 License.[38]

high bioavailability enables the use of high doses of oral collagen supplementation—ideally at least five grams—as suggested by the limited existing literature in non-predatory journals to harness the powerful biological properties of these collagen fragments for skin regeneration with low antigenic potential and minimal risks of Type 1 immediate hypersensitivity.[7]

Predicting Differences in Clinical Efficacy Between Collagen Hydrolysates from Marine Organisms and Land Mammals

Elucidating the issue is not straightforward, as high-level studies in humans are scarce for both classes of compounds, and there are no head-to-head comparisons. For instance, unlike the growing body of well-designed human studies on hydrolyzed marine collagens, it is notable that, as of early November 2025, there are no new papers on hydrolyzed bovine collagen in aesthetics indexed in PubMed, but only three papers in orthopedics.[40–42]

Beyond the impossibility of predicting differences in clinical efficacy, the lack of peer-reviewed, indexed studies limits a balanced discussion of the merits and liabilities of hydrolyzed marine collagens, including any conflicting evidence. The academic credibility of papers published in non-indexed, non-peer-reviewed journals may be low, potentially due to promotional bias. What can be tentatively said without hard evidence is that hydrolyzed collagen fragments from land mammals, due to their somewhat less dependable bioavailability compared with marine collagen fragments, would probably require even higher-dose formulations than marine fragments. However, without clinical pharmacology studies investigating the dose-effect curves of the two types of collagen hydrolysates—a research deficiency that deserves addressing—this remains an open question. Still, mimicking the effects of physiological matrikines, the biological rationale for their skin rejuvenating effects is solid, as summarized in Figure 12.[13]

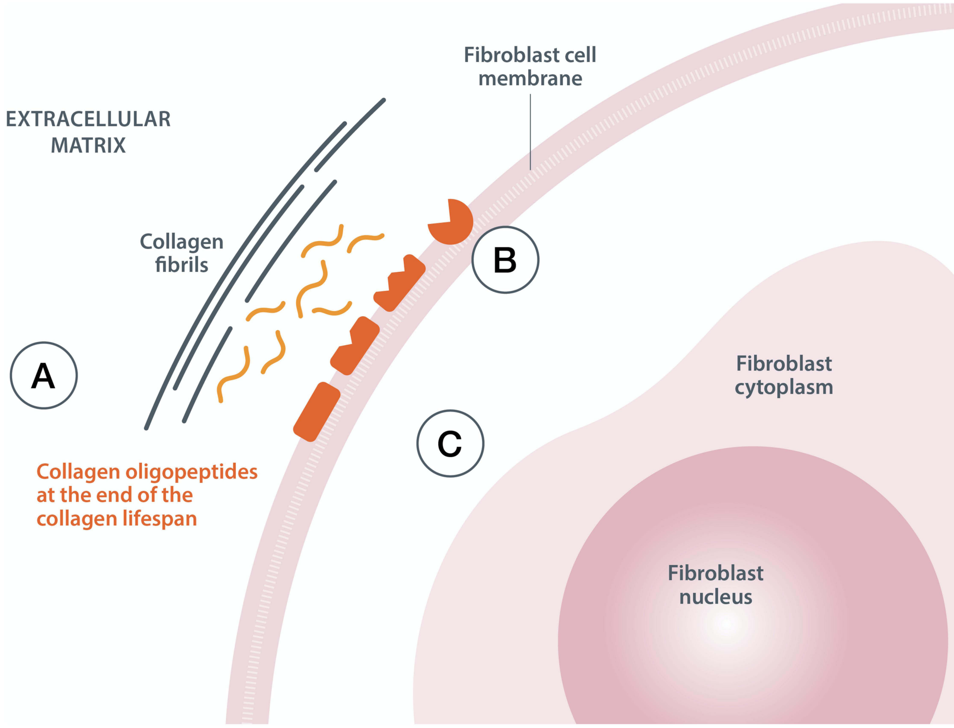


Figure 12 The likely effects of hydrolyzed marine collagens on fibroblasts mimicking and complementing those of physiological matrikines at the end of the lifespan of native collagen in dermis and subdermal tissues. (A): At the end of their lifespan, on average, 140–160 days in the skin, collagen fibers are degraded into oligopeptides and then recyclable, constituent amino acids by matrix zinc-dependent metalloproteinases. Some collagen oligopeptides with specific sequences of amino acids are matrikines that interact with specific binding sites on the fibroblast cell membrane, prompting the fibroblast to produce new collagen fibers. (B): Fibroblast cell surface receptors of chemokines, cytokines, ion channels, and growth factors, and physiological binding sites of matrikines, including specific collagen fragments. (C): Since several well-known matrikines exhibit high homology to marine collagen fragments, marine collagen hydrolysates act passively by replenishing the pool of physiological collagen matrikines and supporting their physiological positive feedback loop, inducing fibroblasts to produce new collagen.[12,13]

Is the Emphasis on Non-Human Preclinical Studies a Bias of This Review?

The debate over the predictive value of animal and in vitro studies for humans has persisted for decades.[43] The emphasis on preclinical studies in this review is an important issue worth further discussion. Regarding hydrolyzed marine collagens, non-human studies cannot directly substantiate clinical benefits in medical aesthetics, but their predictive potential in anticipating possible clinical benefits cannot be denied. Animal and in vitro studies provide the rationale for further human research, as long as they are methodologically sound and have well-described procedures to ensure replication, as was the case with those reviewed by the authors.[43]

The focus on non-human studies was unavoidable because there are still few methodologically sound human studies published in indexed, reputable journals. The authors are confident that they reviewed all relevant human studies that meet rigorous methodological standards and were published in respected journals with realistic outcomes. Especially for human studies, the authors specifically considered only studies on hydrolyzed marine collagen published in PubMed-indexed, peer-reviewed journals with a reasonable impact factor. This approach may have overlooked some occasional human studies with honest results, including those published on corporate websites, but it reduced the risk of over-estimating aesthetic benefits and minimized potential promotional bias.

Moreover, preclinical studies are indispensable for elucidating the biological dynamics underlying the effects of marine hydrolysates on fibroblasts. The prevention by mitomycin C—which halts the cell cycle in the G2 phase without affecting cell migration—suggests that the hydrolyzed peptides specifically influence fibroblast growth.[44] Likewise, the beneficial effects on skin hydration are active rather than passive, involving the activation of the HAS2 transcription pathway in human dermal fibroblasts and the stimulation of hyaluronic acid synthesis.[36]

Additional supplementation with vitamin C may be helpful because it promotes the hydroxylation of proline and lysine—both essential for synthesizing the collagen precursor procollagen—and boosts collagen mRNA production by fibroblasts.[45] However, the benefits observed in the limited clinical studies so far still need to be better defined and quantified.[46]

Aside from the extensive preclinical documentation already available on the biological effects studied at the molecular level, the well-designed clinical literature on the actual aesthetic benefits of hydrolyzed marine collagens remains limited. The short-term follow-up of the few rigorously conducted published studies is another concern, emphasizing the urgent need for robust long-term studies to assess the durability of the aesthetic benefits. Clarifying the long-term safety of hydrolyzed marine collagens is also essential, as this information is currently lacking. The authors are conducting a long-term study to address this issue.

Can Medical Aesthetics Practitioners Glean Practical Insights from This Review?

The limited pool of literature examined—partly due to the still scarce indexed literature on hydrolyzed marine collagens, especially as ingredients in nutritional supplements and cosmeceuticals—can be seen as a weakness of the review. However, choosing to identify and discuss only peer-reviewed articles from reputable journals should contribute to a solid and trustworthy knowledge base on these relatively new ingredients, benefiting aesthetics specialists.

In summary, the promising preliminary findings described in the review are that hydrolyzed marine collagen fragments may develop their anti-aging and regenerative properties throughout the body. However, suggesting rigorous recommendations for aesthetic medicine practitioners regarding ideal doses, subjects, or age ranges that are most likely to benefit is not straightforward at the moment because the accumulated evidence is still limited. The evidence of a lack of serious safety and allergic issues seems solid in correctly designed studies conducted so far, probably suggesting that there should be no serious contraindications to short cycles of intake of the new biorevitalising agent, eg, two or three months twice yearly, used in monotherapy or in combination with other skin rejuvenating options.

Conversely, defining the ideal age for maximum efficacy is more difficult. The efficacy shown in clinical studies may have benefited from the late youth to mid-age age range of most individuals enrolled in studies. Due to the central role of dermal and subdermal fibroblasts, advanced fibroblast attrition is likely to emerge in future studies as a primary determinant of the biorevitalising effects of marine collagen hydrolysates. Fibroblast attrition refers to a decrease in fibroblast density, increased apoptosis, and reduced proliferative potential, as well as a decrease in stem cell populations and the accumulation of senescent fibroblasts that release a mixture of inflammatory mediators, known as the Senescence-Associated Secretory Phenotype (SASP).[47–50] A recent histological analysis of sun-protected skin from young (18–29 years) and elderly (80 years or older) individuals demonstrated a 35% reduction in fibroblast density in aged skin, a 68% reduction in type I procollagen content, and a 30% decrease in fibroblast collagen synthetic capacity.[47] The rejuvenating effects of marine collagen hydrolysates could thus be less notable in significantly aged or severely photodamaged skin, but the evidence is still missing.

In conclusion, the benefits of the new class of marine collagen hydrolysates may include external effects, such as reversing skin aging, as discussed in this review, and internal benefits like supporting osteoarticular health and influencing metabolic processes, as suggested by preliminary accumulating evidence.[7] It is a future that may have already started to unfold, but more experimental and human studies, including long-term research, are needed to support this promising evidence.

Data Sharing Statement

The minutes of board discussions are archived and can be provided upon reasonable request from the Corresponding Author.

Ethical Statement

The submitted review addresses previously published information, thus waiving any formal preliminary requirement for Institutional Review Board approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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