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Fish Scale-Derived Collagen for Cosmetic, Nutricosmetic, and Biomedical Applications: Processing, Material Forms, and Evidence

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ABSTRACT

Fish scales are a well-established source of type I collagen and represent a potential route for recovering higher-value materials from fish-processing by-products. However, fish-scale collagen is often treated as a single material even though processing can generate products with markedly different structures, functions, and levels of supporting evidence. This narrative review examines fish-scale-derived collagen across the source-processing-material form-property-application-evidence continuum, with emphasis on cosmetic, nutricosmetic, and biomedical uses. Four material categories are distinguished: purified collagen, collagen peptides or hydrolysates, collagen-containing composites, and retained whole-scale collagenous matrices. Available studies show that fish species, scale composition, demineralization, extraction, hydrolysis, and material modification influence collagen recovery, structural integrity, thermal behavior, fibril formation, and downstream performance. For skin-related applications, several controlled human studies support defined orally administered fish-scale collagen peptide preparations for selected hydration, elasticity, and wrinkle-related outcomes, whereas controlled human evidence for topical application remains limited. Biomedical evidence is most developed for wound-healing materials, while bone, oral, periodontal, and corneal applications have progressed through cell-based and animal studies. Many favorable outcomes, however, involve composite materials or retained scale matrices and cannot be attributed to collagen alone. Translation remains constrained by raw-material heterogeneity, inconsistent extraction and yield reporting, incomplete product-specific safety assessment, sterilization and manufacturing requirements, limited human biomedical evidence, and insufficient environmental and economic evaluation of scale-up. Fish-scale collagen should therefore be considered a family of application-dependent materials rather than a uniform alternative collagen source.

Keywords: fish scales, collagen peptides, nutricosmetics, wound healing, tissue engineering

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1. INTRODUCTION

Fish processing produces a range of by-products, including skin, bones, scales, heads, viscera, and frames. Several of these fractions contain proteins and minerals that can be recovered for higher-value uses. Collagen is especially relevant because it can be obtained from multiple fish-processing by-products and converted into materials for food, cosmetic, pharmaceutical, and biomedical applications [1]. Fish scales are distinctive because their collagen-rich organic matrix is closely associated with a mineral phase, allowing them to serve either as a collagen source or, after suitable processing, as a structured collagenous material [2,3].

Although type I collagen has been isolated from the scales of many freshwater and marine fishes, the resulting materials are not uniform. Species, scale composition, demineralization, extraction route, enzymatic treatment, and post-extraction modification can all affect structural integrity, solubility, thermal behavior, fibril formation, molecular size, and downstream performance. These variables need to be considered when results from different studies are compared.

Fish-derived collagen is also being explored as an alternative to conventional bovine and porcine sources, particularly where mammalian materials raise cultural, religious, or sourcing concerns. This diversification does not, however, show that fish-scale collagen is inherently safer, more biocompatible, or more sustainable. Such comparisons depend on purification, material performance, manufacturing requirements, resource use, and the intended application. By-product valorization and environmental superiority should therefore be treated as separate questions.

The term "fish-scale collagen" can refer to materially different products. This review distinguishes four categories: purified collagen (PC), which retains a predominantly native collagen structure; collagen peptides or hydrolysates (CP), produced by hydrolysis; collagen-containing composites (CC), in which scale collagen is combined with other functional components; and whole-scale collagenous matrices (WM), which retain part of the original scale architecture after processing. These forms differ in organization, function, and evidentiary interpretation.

This distinction is essential because peptide-based skin studies, collagen scaffolds, engineered composites, and retained corneal matrices address different material functions. Evidence from one class should therefore not be generalized automatically to another.

Several recent reviews have addressed fish-derived collagen and fish-scale valorization. Gaikwad and Kim [1] reviewed extraction of collagen from multiple fish by-products and its broad applications. Patwary et al. [2] focused on freshwater fish scales but considered collagen together with gelatin and hydroxyapatite across several industrial uses. Dong et al. [3] examined fish scales more broadly as multifunctional natural biomaterials. A remaining need is therefore not another general catalogue of fish-scale uses, but an integrated analysis of how source and processing determine material form and properties, and how these in turn influence the strength of evidence for specific applications.

This narrative review therefore examines fish-scale-derived collagen across the source-processing-material form-property-application-evidence continuum. It considers how species, pretreatment, demineralization, extraction, hydrolysis, and subsequent material modification affect collagen properties; compares evidence for topical, oral, and biomedical uses; and interprets findings according to material class and stage of evidence. The review also identifies limitations in standardization, safety, manufacturing, sterilization, scale-up, and translation.

2. RESEARCH METHODOLOGY

Literature for this narrative review was identified through targeted searches of PubMed and major academic publisher platforms, supplemented by searches used to retrieve primary studies identified from relevant review articles and to verify bibliographic metadata and DOI information.

Searches were conducted up to 12 October 2026 using combinations of terms related to "fish scale" or "fish scales" with collagen, type I collagen, extraction, demineralization, hydrolysis, collagen peptide, physicochemical characterization, cosmetic, skin, topical, wound healing, scaffold, tissue engineering, bone, periodontal, and corneal applications. No lower publication-date limit was imposed because early studies were relevant to the development of fish-scale collagen research.

Priority was given to peer-reviewed primary studies in which collagen, collagen peptides, or collagenous matrices were explicitly derived from fish scales. Studies based exclusively on collagen from fish skin, bone, or other tissues were not considered direct evidence for fish-scale applications, although selected studies were retained when they provided necessary methodological, safety, or environmental context. Relevant review articles were used primarily to establish the literature landscape and to identify primary studies rather than as substitutes for available experimental evidence.

Because this study was designed as a narrative review, the search supported critical and thematic synthesis rather than exhaustive systematic study identification. Formal systematic-review procedures, PRISMA-based screening, quantitative evidence grading, and meta-analysis were therefore not performed. For interpretative purposes, studies were distinguished according to material form (purified collagen, collagen peptides or hydrolysates, collagen-containing composites, and retained whole-scale collagenous matrices) and according to experimental stage from material characterization to human investigation. These categories were used to clarify the maturity and applicability of the evidence rather than as a formal methodological quality score.

3. RESULTS AND DISCUSSION

3.1. Fish Scales as a Source of Collagen

3.1.1. Structural Organization and Composition

Fish scales are composite tissues rather than uniform protein residues. In many teleosts, a collagen-rich organic matrix is integrated with a mineral phase composed largely of calcium phosphate minerals. The two components are arranged hierarchically, and the degree of mineralization, fibril orientation, and lamellar organization can vary across regions of the scale and among species.

Detailed structural work on red sea bream (*Pagrus major*), for example, demonstrated a layered scale architecture containing densely organized collagen fibers and a mineral phase characterized as calcium-deficient hydroxyapatite [4]. More recent comparative analyses have emphasized that scale type, degree of mineralization, collagen orientation, and thickness of structural layers can differ considerably among fish species [3].

This collagen-mineral association has direct implications for processing. Mineral removal is generally required before efficient extraction of purified collagen because the fibrillar protein is physically embedded within the scale matrix. Conversely, applications based on retained whole-scale matrices may deliberately preserve part of the native collagen-mineral architecture. Thus, fish scales can be used through two fundamentally different routes: disassembly to recover collagen molecules or controlled processing to preserve a collagenous structural template.

3.1.2. Type I Collagen in Fish Scales

Type I collagen is the principal collagen reported from many fish scales and generally contains two alpha-1 chains and one alpha-2 chain. Studies of rohu, catla, Nile tilapia, and carp have confirmed type I identity and retention of major triple-helical features after extraction [5-7]. Amino-acid composition contributes to helix stability, and Ikoma *et al.* [8] showed that collagen from *P. major* and *O. niloticus* differed in physical properties despite sharing the same collagen type. Collagen classification alone therefore does not establish functional equivalence.

3.1.3. Species-Dependent Variability

Collagen composition and performance can vary among fish species, including thermal behavior, extraction response, solubility, and fibril formation. Yet biological differences are difficult to separate from methodological effects because studies often use different pretreatments, extraction conditions, purification procedures, and analytical methods.

Accordingly, broad labels such as "marine collagen" or "freshwater collagen" have limited predictive value. Species identity, collagen preparation, and processing history must be considered together when assessing suitability for cosmetic or biomedical use.

Yield comparisons add another source of uncertainty. Reported recovery depends on mineralization, pretreatment, collagen fraction, process severity, and the denominator used for calculation. Table 1 therefore reports yields using the basis given in each source rather than treating them as directly comparable extraction efficiencies.

3.2. Recovery and Processing of Fish-Scale Collagen

3.2.1. Raw-Material Preparation and Demineralization

Collagen recovery from fish scales usually starts with removal of non-collagenous material and reduction of the mineral phase. Typical operations include washing, size reduction, alkaline pretreatment, and demineralization with acids or chelating agents. These steps improve access to the collagenous matrix and influence the efficiency of subsequent extraction.

Pati *et al.* [5] showed progressive demineralization of *L. rohita* and *C. catla* scales during EDTA treatment, while Nagai *et al*. [9] found that intact scales were poorly solubilized in acetic acid before decalcification and structural disruption. These findings highlight matrix accessibility as a key determinant of subsequent extraction; pretreatment conditions therefore need to be reported clearly for meaningful comparison.

3.2.2. Acid-Soluble Collagen

Acid extraction, most often with dilute organic acids such as acetic acid, is commonly used to solubilize collagen while preserving much of its molecular structure. Because the mineralized matrix restricts solvent access, demineralization usually precedes acid extraction in fish scales.

Reported ASC yields vary markedly among species and protocols. Matmaroh *et al.* [10], for example, reported 0.46% on a dry-weight basis from spotted golden goatfish scales. Such values should not be ranked across studies without considering starting material, pretreatment, extraction conditions, and calculation basis. Under sufficiently mild conditions, acid extraction can preserve type I collagen, although more strongly cross-linked collagen may remain insoluble.

3.2.3. Pepsin- and Enzyme-Assisted Extraction

Pepsin can improve collagen solubilization by cleaving telopeptide regions involved in intermolecular cross-linking while leaving much of the triple-helical domain intact. This is particularly useful when demineralized scales remain resistant to acid extraction.

Nagai *et al*. [9] reported comparatively high recovery after combining decalcification, structural disaggregation, and limited pepsin digestion. Matmaroh et al. [10] likewise obtained a higher PSC than ASC yield from spotted golden goatfish scales, whereas Jaziri et al. [11] found no significant ASC-PSC yield difference in parrotfish. Pepsin therefore does not universally improve recovery; its effect depends on species, cross-linking, pretreatment, and enzyme conditions.

Because pepsin modifies terminal regions of collagen molecules, ASC and PSC from the same species may also differ in solubility, aggregation, and fibrillogenesis despite retaining the general type I structure.

3.2.4. Physical and Intensified Extraction

Conventional extraction may involve prolonged chemical treatments. Physical intensification has therefore been explored to improve access to the collagenous matrix or reduce processing time. Huang *et al.* [12] developed an extrusion-hydro-extraction process for tilapia scales and reported approximately two- to three-fold higher protein extraction yields after extrusion compared with non-extruded controls under the conditions evaluated.

Increased recovery alone, however, does not establish process superiority. Mechanical energy, pressure, elevated temperature, ultrasound, or other intensified treatments can alter collagen structure if conditions are too severe. Process evaluation should therefore consider both recovery efficiency and retention of properties required for the intended application.

3.2.5. Hydrolysis and Collagen Peptides

Hydrolysis serves a different purpose from native collagen extraction. Enzymatic or hydrothermal treatment intentionally converts collagen into lower-molecular-weight peptides, altering solubility, diffusion, molecular recognition, and potential bioactivity.

Chai *et al*. [13] generated collagen peptides from fish scales through enzymatic hydrolysis and evaluated peptide fractions in fibroblast, penetration, and topical skin studies. More recent topical formulations have similarly used hydrolyzed rather than native collagen [14]. Shen *et al.* [15] further demonstrated that fish-scale collagen peptide fractions of different molecular sizes produced different wound-related responses in a mouse model.

These results must remain separate from evidence concerning intact type I collagen. Native collagen and low-molecular-weight peptides have fundamentally different structural and technological functions.

3.2.6. Emerging Extraction Approaches

Natural deep eutectic solvents (NADES) and ultrasonication have recently been explored as alternatives to prolonged conventional extraction. Hamdi *et al.* [16] recovered type I collagen from sea bass scales using NADES-assisted ultrasonication while retaining triple-helical and fibril-forming characteristics, and Kara *et al.* [17] reported similar structural preservation with a citric acid-xylitol-water NADES system.

NADES-assisted and ultrasound-assisted approaches may shorten processing or reduce reliance on conventional extraction conditions, but those features alone do not demonstrate environmental superiority. Water and energy demand, solvent preparation and recovery, waste generation, purification, scale-up efficiency, and life-cycle performance still need to be considered.

Table 1. Selected Fish-Scale Collagen Sources, Processing, and Key Properties.

Fish species/source	Processing	Fraction	Reported yield/basis	Key identification and properties	Ref.
Sardine; red sea bream; Japanese sea bass	Decalcification + structural disaggregation; limited pepsin digestion	PSC	50.9%, 37.5%, 41.0%; dry-weight basis	Type I heterotrimer, (α1)2α2; species-dependent thermal properties	[9]
Labeo rohita; *Catla catla*	EDTA demineralization; acid extraction	Type I collagen	~5 wt.%	SDS-PAGE, FTIR, CD, amino acids; Td ≈36.5 °C	[5]
Parupeneus heptacanthus	Scale preparation + demineralization; acetic acid ± pepsin	ASC; PSC	0.46% ASC; 1.20% PSC; dry weight	Type I; α1/α2, β/γ; triple helix retained; Tmax 41.58/41.01 °C	[10]

Nile tilapia, *Oreochromis niloticus*	Demineralization + scale preparation; pepsin-assisted extraction	PSC	Not ranked across studies	Type I (α1)2α2; FTIR/XRD; Td ≈32.1 °C; cell attachment/proliferation in gel	[6]
Tilapia, *Oreochromis sp.*	NaOH pretreatment, drying/milling; extrusion–hydro-extraction	Type I-rich extract	~2–3× non-extruded control	FTIR, SDS-PAGE, MW analysis; extraction intensification	[12]
C. catla; L. rohita	Demineralization; acid + pepsin extraction	ASC; PSC	2.80–4.11% w/w	Type I collagen; Td 35.9–37.7 °C; acidic solubility; fibrils	[7]
Parrotfish, *Scarus sordidus*	Scale preparation+demineralization; acetic acid ± pepsin	ASC; PSC	1.17 and 1.00 g/100 g	Type I; triple helix retained; Tmax 36.22–37.78 °C; acidic/low-NaCl solubility	[11]
European sea bass	Scale preparation; NADES + ultrasonication	Type I collagen	Not directly comparable	Triple helix retained; fibril formation; cytotoxicity/hemolysis screening	[16]
Red mullet; gilthead sea bream; European sea bass	Scale preparation; citric acid–xylitol–water NADES	Type I collagen	Not directly comparable	SDS-PAGE, FTIR, XRD; later ginger systems represent composite effects	[17]

Notes: ASC, acid-soluble collagen; PSC, pepsin-soluble collagen; EDTA, ethylenediaminetetraacetic acid; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; FTIR, Fourier-transform infrared spectroscopy; CD, circular dichroism; XRD, X-ray diffraction; Td, denaturation temperature; Tmax, maximum thermal-transition temperature; NADES, natural deep eutectic solvent. Reported yields are reproduced according to the calculation basis used in the original studies and should not be interpreted as directly comparable extraction efficiencies unless equivalent starting materials, pretreatments, and calculation methods were used. Td and Tmax are retained according to the terminology of the original studies and should not be treated as interchangeable measurements.

3.3. Structural, Physicochemical, and Biological Characteristics

3.3.1. Molecular Identity and Structural Integrity

Recovering collagen-rich protein does not, by itself, show that native collagen structure has been preserved. For applications that depend on fibril formation, gelation, membranes, or scaffolds, molecular identity and structural integrity are more informative than yield alone.

Most studies of purified fish-scale collagen identify type I collagen through SDS-PAGE together with spectroscopic or structural analyses such as FTIR, circular dichroism, or X-ray diffraction. Pati et al. [5], El-Rashidy et al. [6], and Pal and Suresh [7] each reported characteristic type I collagen profiles and evidence that major features of the triple-helical organization were retained after extraction.

Confirming type I collagen is only one step in assessing material suitability. Preparations with similar chain patterns may still differ in telopeptide content, aggregation, solubility, thermal response, fibril formation, and cell interaction. Structural identification should therefore be followed by application-relevant physicochemical and biological testing.

3.3.2. Thermal Stability

Thermal stability matters because loss of triple-helical organization can affect fibrillogenesis, gel behavior, mechanical performance, and stability near physiological temperature. Reported values for fish-scale collagen vary substantially among species and preparations.

Ikoma *et al.* [8] reported different denaturation behavior for type I collagen from red sea bream and tilapia scales. Pati *et al.* [5] reported a denaturation temperature of approximately 36.5 °C for collagen isolated from rohu and catla scales, whereas El-Rashidy *et al.* [6] reported approximately 32 °C for pepsin-solubilized Nile tilapia scale collagen. Pal and Suresh [7] reported values in the mid-to-upper 30 °C range for carp scale collagen fractions.

Direct comparison of reported thermal values requires caution because studies do not always use the same terminology or analytical method. Denaturation temperature, melting temperature, and maximum transition temperature should be reported as defined in the original source and interpreted in relation to the intended application.

For fibrillar scaffolds or gels intended to function near physiological temperature, limited thermal stability may require additional stabilization. For hydrolyzed peptide formulations, in contrast, preservation of native triple-helical organization is no longer the principal requirement. Cross-linking can increase the stability of collagen-based constructs, but the resulting properties belong to the modified material rather than to purified collagen alone.

3.3.3. Solubility, Fibrillogenesis, and Material-Forming Capacity

Solubility influences both collagen purification and subsequent fabrication. Fish-scale collagen generally exhibits greater solubility under acidic conditions, whereas increasing ionic strength can promote aggregation and decrease solubility. Pal and Suresh [7], for example, reported acid-dependent solubility and the ability of carp-scale collagen preparations to form fibrils under appropriate conditions.

Fibrillogenesis is particularly relevant for biomaterials because it recreates part of the supramolecular organization characteristic of extracellular-matrix collagen. Hamdi *et al.* [16] similarly reported fibril formation after NADES-assisted recovery of sea bass scale collagen.

Fibril formation alone does not ensure that a scaffold will perform adequately. Porosity, water uptake, mechanical resistance, enzymatic degradation, contraction, and stability also depend on collagen concentration, fabrication conditions, drying, cross-linking, and any added components. This is one reason many biomedical systems move beyond purified collagen to engineered composites.

Whole-scale collagenous matrices differ further because their architecture is not reconstructed from solubilized collagen. Instead, processing preserves part of the original fibrillar organization of the scale. Their optical or mechanical properties therefore cannot be extrapolated to purified collagen.

3.3.4. Cytocompatibility, Degradation, and Preliminary Biocompatibility

Several studies show that fish-scale-derived collagen can support cell adhesion and proliferation under defined experimental conditions. El-Rashidy et al. [6], for example, reported attachment and proliferation of BHK-21 cells within Nile tilapia collagen gels. Hamdi *et al.* [16] incorporated cytotoxicity and hemolysis screening into characterization of collagen recovered using NADES-assisted ultrasonication.

These assays are useful for preliminary screening, but cytocompatibility does not establish long-term biocompatibility, low immunogenicity, or clinical safety.

Sugiura *et al.* [18] extended the evidence to an in vivo model by comparing tilapia-scale collagen and porcine collagen after fabrication into cross-linked sponges. Rabbit implantation showed relatively limited inflammatory responses under the conditions tested, while material behavior depended partly on cross-linking and scaffold preparation.

Biodegradation should also be interpreted relative to application. Rapid degradation may benefit some temporary wound matrices but undermine scaffolds that require prolonged structural support. Excessive stabilization can have the opposite problem. Appropriate degradation therefore depends on the function of the finished material.

Taken together, the structural, physicochemical, and biological behavior of fish-scale collagen reflects the combined influence of species, processing, collagen fraction, molecular form, and material engineering. Application studies therefore need to be interpreted in relation to the specific material that was actually tested.

3.4. Cosmetic and Nutricosmetic Skin Applications

3.4.1. Material Form and Rationale for Skin-Related Use

Skin-related applications of fish-scale collagen are dominated by hydrolyzed products rather than intact fibrillar collagen. Native collagen is a large macromolecular assembly, whereas hydrolysis produces lower-molecular-weight peptides with different solubility, transport, and biological behavior. Evidence concerning peptides should therefore not be generalized to native collagen.

Fish-scale collagen peptides may function as formulation ingredients and, depending on molecular characteristics, may also influence fibroblast or extracellular-matrix-related responses. The resulting evidence can be divided into topical formulation and delivery, cell-based activity, topical human use, and orally administered skin-directed peptide preparations.

3.4.2. Topical Formulation and Skin Delivery

Chai *et al.* [13] investigated fish-scale collagen peptide fractions of different molecular sizes using diffusion experiments and topical application. Their findings showed that penetration was not explained by molecular mass alone, indicating that peptide conformation and physicochemical behavior also affect transport.

Zainol *et al.* [14] subsequently incorporated hydrolyzed Nile tilapia scale collagen of approximately 1 kDa into a water-in-oil cream and evaluated formulation characteristics, fibroblast responses, ex vivo rat-skin permeation, and preliminary safety. The formulated system increased peptide permeation and skin retention relative to aqueous collagen controls under the experimental conditions.

These experiments support the topical delivery potential of hydrolyzed fish-scale collagen but do not show that native collagen readily crosses intact human skin. The observed permeation is better interpreted as a property of both the peptide preparation and the delivery system.

3.4.3. Cellular and Photoaging-Related Evidence

Chai *et al.* [13] reported increased fibroblast proliferation and procollagen type I production after treatment with fish-scale collagen peptides under in vitro conditions. These results provide mechanistic support for skin-related activity but do not directly establish wrinkle reduction or dermal regeneration in humans.

Yao *et al.* [19] examined hydrophobic peptide fractions derived from *Oreochromis mossambicus* scale collagen peptides in UVA-damaged human fibroblasts. The selected fraction showed antioxidant and elastase-related effects, promoted fibroblast proliferation and migration, increased collagen I and elastin-related responses, and reduced expression of several matrix metalloproteinases under the conditions evaluated.

Hydrolysis and peptide fractionation can therefore generate preparations with distinct biological activities. Even so, cell-based photoaging models remain mechanistic evidence and should not be interpreted as clinical anti-aging efficacy.

3.4.4. Human Topical Evidence

The principal human topical evidence remains Chai *et al.* [13], in which 62 women used fish-scale collagen peptide essences twice daily for 30 days, and increases in facial moisture and relative elasticity were reported.

Because the study lacked the design of a modern randomized vehicle- or placebo-controlled cosmetic trial, it provides preliminary human topical evidence rather than definitive proof of anti-aging efficacy. This remains a clear gap compared with the larger body of formulation, permeation, and cell-based research.

3.4.5. Oral Collagen Peptides and Human Skin Outcomes

Human evidence is more developed for orally administered fish-scale-derived collagen peptides. Koizumi *et al.* [20] conducted a randomized, double-blind, placebo-controlled study using 3 g/day of fish-scale-derived collagen peptides for 12 weeks. Improvements were reported in selected periorbital wrinkle, moisture, and elasticity parameters.

Lee *et al*. [21] evaluated 1.65 g/day of a defined fish-scale-derived collagen peptide preparation in a randomized, double-blind, placebo-controlled study involving 100 completers. Improvements in hydration and desquamation appeared earlier in the intervention, while wrinkle and elasticity outcomes differed at later time points.

Seong *et al.* [22] Similarly evaluated 2 g/day of low-molecular-weight collagen peptides derived from Nile tilapia scales in a randomized, double-blind, placebo-controlled study. Several wrinkle-, elasticity-, hydration-, pigmentation-, and erythema-related measurements differed from placebo after supplementation.

Together, these trials show controlled human evidence for defined oral fish-scale collagen peptide products. They should still be interpreted separately from topical studies because oral peptides undergo digestion, absorption, systemic distribution, and metabolism, whereas topical products depend on skin-barrier penetration and local formulation behavior.

3.4.6. Overall Strength and Limitations of Skin-Related Evidence

Skin-related evidence is asymmetric: several controlled human studies support defined orally administered fish-scale collagen peptide preparations, whereas controlled human evidence for topical use remains limited.

Interpretation is also product-specific. Species, hydrolysis method, molecular-weight distribution, dose, formulation, study population, and endpoints differ among trials, so findings from one standardized preparation should not automatically be generalized to other fish-scale collagen hydrolysates. Independent replication would further strengthen the evidence base.

Claims for cosmetic and nutricosmetic use should therefore identify the material form, administration route, dose or formulation, and level of supporting evidence. Table 2 summarizes the main differences between topical and oral studies.

Table 2. Cosmetic and Nutricosmetic Evidence for Fish-Scale Collagen Peptides.

Source/material	Route/ dose	Study design/ model and evidence	Main outcomes	Main limitation	Ref.
Fish-scale collagen peptide fr actions	Topical; 5%, 7%, or 10% essence	In vitro + diffusion + human application; 62 women; 30 d (E5)	Procollagen-related responses; p eptide penetration; increased moisture/elasticity	Not a modern randomized vehicle-controlled trial	[13]
Fish-scale-derived collagen p eptides	Oral; 3 g/day	Randomized double-blind placebo-controlled trial; 71 completers; 12 wk (E 6)	Improved selected wrinkle, moisture, elasticity measures	Single standardized p reparation/ population	[20]
Fish-scale-derived collagen p eptide preparation	Oral; 1.65 g/day	Randomized double-blind placebo-controlled trial; 100 completers; 12 wk (E6)	Improved hydration/ desquamation; later wrinkle/ elasticity outcomes	Product-specific preparation	[21]
Nile tilapia-scale low-MW pe ptides	Oral; 2 g/day	Randomized double-blind placebo-controlled trial; n=100; 12 wk (E6)	Improved selected wrinkle, elasticity, hydration, melanin, er ythema measures	Product- and population-specific	[22]

Oreochromis mossambicus scale peptide fraction	Mechanistic; hydrophobic peptide fraction	UVA-damaged human fibroblasts (E2)	Antioxidant/elastase effects; collagen I/elastin responses; decreased MMPs	Cell-based evidence only	[19]
Nile tilapia-scale hydrolyzed collagen (~1 kDa)	Topical; water-in-oil cream	Formulation + fibroblasts + ex vivo rat-skin permeation + preliminary animal safety (E2–E4)	Formulation feasibility; peptide permeation/retention; preliminary compatibility	No controlled human topical efficacy trial	[14]

Notes: MW, molecular weight; E2, cell-based evidence; E4, animal/preclinical evidence; E5, human application/observational evidence; E6, controlled human study. Evidence stages indicate experimental progression and do not constitute a formal methodological quality score. Oral and topical evidence should be interpreted separately because their exposure routes and mechanisms differ substantially.

3.5. Biomedical Applications

3.5.1. Wound Healing and Wound-Dressing Materials

Among biomedical applications, wound healing has the broadest preclinical evidence base for fish-scale-derived collagen. The literature nevertheless spans very different materials, including purified sponges, chemically modified matrices, polymer composites, multifunctional hydrogels, and collagen peptides, so their outcomes should not be treated as evidence for a single uniform material.

Pal *et al.* [23] isolated type I collagen from *Cirrhinus cirrhosus* scales and fabricated collagen sponges. The material supported fibroblast and keratinocyte growth and was subsequently evaluated in a rat full-thickness wound model, where treatment was associated with accelerated repair. This study is particularly useful because it links collagen characterization, scaffold fabrication, cell response, and in vivo wound evaluation within the same experimental system.

Wang *et al.* [24] developed chemically modified and cross-linked fish-scale collagen patches and evaluated their tissue integration after implantation. The material supported cellular infiltration and vascular and lymphatic growth. Because the study used implantation rather than an open wound model, it supports regenerative integration and vascularization rather than direct evidence of accelerated wound closure.

Shi *et al.* [25] compared porous fish-scale collagen and porcine collagen sponges in a rabbit burn model. Both collagen materials produced favorable healing-related outcomes compared with conventional dressings. However, the study used a very small number of animals with multiple wounds per animal, limiting the independence of experimental units. The findings are therefore encouraging, comparative preclinical evidence rather than proof of equivalence.

Composite systems demonstrate additional functionality but create attribution problems. Pal *et al.* [26] incorporated fish-scale collagen into a hierarchical polycaprolactone (PCL)-chitosan scaffold and reported favorable cellular and burn-wound responses. Feng *et al.* [27] developed an aminated fish-scale collagen-oxidized alginate hydrogel containing antimicrobial peptides and observed antibacterial activity and improved wound-related outcomes in a rat model. These responses belong to the complete engineered systems and cannot be assigned solely to collagen.

Li *et al*. [28] developed a collagen-dominant sponge from *Alosa sapidissima* scales and reported hemostatic activity together with neovascularization, granulation, re-epithelialization, and remodeling in a rat full-thickness wound model. This provides comparatively informative recent preclinical evidence for a collagen-dominant system, although human efficacy remains untested.

Fish-scale collagen peptides represent another distinct strategy. Shen et al. [15] reported wound-related effects of collagen peptide preparations delivered by topical and oral routes in mice, with lower-molecular-weight fractions showing stronger responses among the preparations tested. These results suggest possible bioactivity of selected peptide fractions but cannot be generalized to intact collagen scaffolds. The wound-healing literature now extends from cellular studies to several animal models, but it remains predominantly preclinical. Differences in species, formulation, wound model, comparator, and outcome measurement continue to limit direct comparison among studies.

3.5.2. Bone, Oral, and Periodontal Tissue Regeneration

Fish-scale-derived collagen has also been studied in oral and mineralized-tissue engineering. These applications range from purified collagen substrates to polymer composites and retained collagen-mineral scale matrices.

Tang and Saito [29] compared purified tilapia-scale type I collagen with porcine collagen using odontoblast-like cells. Both materials supported cell attachment, proliferation, differentiation-related responses, and mineral deposition under the evaluated conditions. These findings support cellular comparability in the specific model but do not establish in vivo or clinical equivalence.

Oh et al. [30] used enzymatically cross-linked tilapia-scale collagen scaffolds with human mesenchymal stem cells and reported osteoblastic differentiation-related responses. The study illustrates the role of scaffold stabilization in converting collagen into a more functional three-dimensional material but remains cell-based evidence.

Oral mucosa studies have frequently used composite systems. Terada *et al.* [31] combined tilapia-scale collagen with chitosan and produced a tissue-engineered oral mucosa equivalent with multilayered epithelial organization. Suzuki *et al*. [32] subsequently developed microstructured fish-scale collagen scaffolds supporting differentiated and stratified oral epithelium, while also identifying contraction and mechanical limitations.

Another strategy retains the natural collagen-mineral organization of the scale. Chen *et al.* [33] developed a fish-scale-derived membrane containing type I collagen and hydroxyapatite and evaluated it against a commercial porcine collagen membrane. The material supported cell adhesion and osteogenic responses in vitro. Its high reported thermal transition should not be compared directly with values for purified collagen because the membrane retains a composite collagen-mineral architecture.

Li *et al.* [34] developed a fish-scale collagen/chitosan nanofibrous membrane with biomimetic hydroxyapatite mineralization. The composite promoted osteogenic responses in vitro and periodontal bone regeneration in a rat defect model. This represents one of the stronger preclinical periodontal studies identified here, but the outcome reflects the combined functions of collagen, chitosan, and hydroxyapatite.

The current evidence therefore supports fish-scale collagen mainly as a component of engineered oral and mineralized-tissue systems, rather than showing that purified collagen alone is an osteogenic therapeutic material.

3.5.3. Corneal Tissue Engineering Using Fish-Scale Collagen and Collagenous Matrices

Corneal applications differ fundamentally from many other biomedical uses because they frequently exploit the retained architecture of processed scales rather than purified collagen alone.

Lin *et al.* [35] demonstrated that decellularization and decalcification could preserve an organized three-dimensional collagen structure capable of supporting corneal-cell proliferation and migration. Krishnan et al. [36] subsequently evaluated fish-scale collagen scaffolds against human amniotic membrane for limbal epithelial culture and obtained favorable cell-growth and handling characteristics.

Optical and implantation properties were examined by van Essen et al. [37]. Fish-scale-derived collagen matrices showed encouraging light transmission, but light scatter and tissue responses varied according to implantation configuration. Some conditions produced haze, inflammation, or partial material deterioration. These findings are important because they demonstrate that the corneal evidence is not uniformly positive.

Yuan et al. [38] reported longer-term implantation of a decellularized and decalcified tilapia-scale matrix in rabbit corneal stromal pockets. The material remained transparent and structurally integrated during the observation period. However, protected stromal-pocket implantation does not reproduce the full demands of corneal replacement.

Van Essen et al. [39] further examined human corneal-cell responses and animal implantation and reported favorable compatibility under the tested conditions. These results support low reactivity of the specific processed matrix but should not be generalized into a claim that fish-scale collagen is universally non-immunogenic.

Chen et al. [40] evaluated a processed tilapia-scale BioCornea as a short-term patch for full-thickness corneal perforation in mini-pigs. The material maintained anterior-chamber integrity during the short follow-up. This supports a temporary sealing function rather than long-term artificial-cornea replacement.

Processed fish scales have also been evaluated as carriers for corneal endothelial cells. Hsueh et al. [41] demonstrated that extracellular-matrix coatings enhanced endothelial-cell adhesion and proliferation on processed scales, indicating that the native scale surface alone was not optimal for all cell types. Li et al. [42] subsequently evaluated corneal endothelial cells seeded onto fish-scale collagen membranes and implanted the constructs into rabbit anterior chambers as a preclinical endothelial-keratoplasty strategy.

Cheng et al. [43] expanded this concept to grass carp scales and reported a processed collagen lamellar matrix with optical, mechanical, and cellular properties relevant to artificial-cornea development.

The corneal literature shows a clear preclinical progression from structural preservation and cell culture to ocular implantation and cell delivery. Most studies, however, involve whole-scale collagenous matrices (WM) rather than purified collagen, and no controlled human corneal evidence was identified. Table 3 summarizes the principal studies by material class, experimental model, and attribution limitation.

Table 3. Representative Biomedical Evidence for Fish-Scale-Derived Collagen.

Application	Source/material (class)	Model/comparator	Main outcome / evidence	Key limitation	Ref.
Biocompatibility / implantation	Tilapia-scale collagen; cross-linked sponge (CC)	Rabbit implantation; porcine collagen comparator	Limited inflammatory response; bioresorption (E4)	Depends partly on cross-linking/ scaffold preparation	[18]
Full-thickness wound repair	*Cirrhinus cirrhosus* collagen sponge (PC)	Fibroblast/keratinocyte culture + rat wound model	Cell growth, epithelial organization, accelerated repair (E4)	Preclinical; species/ preparation specific	[23]
Tissue integration / vascularization	Modified cross-linked fish-scale collagen patch (CC)	Mouse subcutaneous implantation	Cell infiltration; blood/lymphatic vessel growth (E4)	Implantation, not direct wound-closure model	[24]
Burn wound repair	PCL–chitosan scaffold + fish-scale collagen (CC)	Cell studies + rat burn model	Improved integration and healing-related outcomes (E4)	Multi-component scaffold	[26]
Burn wound dressing	Fish-scale collagen porous sponge (PC)	Rabbit burn model; porcine collagen/conventional dressings	Favorable moisture-related and histological outcomes (E4)	Very small animal number; multiple wounds/animal	[25]
Full-thickness wound healing	Aminated collagen + oxidized alginate + antimicrobial peptides (CC)	Cell assays + rat wound model	Antibacterial activity; re-epithelialization; collagen deposition; angiogenesis (E4)	Effect belongs to full hydrogel system	[27]
Hemostasis / wound healing	*Alosa sapidissima* collagen sponge (PC)	Rat full-thickness wound model	Hemostasis; neovascularization; granulation; re-epithelialization; remodeling (E4)	No human wound evidence	[28]
Mineralized-tissue response	Tilapia-scale purified type I collagen (PC)	MDPC-23 cells; porcine collagen comparator	Attachment, proliferation, differentiation-related response, mineralization (E2)	Cell-line evidence only	[29]
Oral mucosa engineering	Tilapia collagen–chitosan scaffold (CC)	Tissue-engineered oral mucosa model	Multilayered epithelial organization (E3)	Composite; ex vivo/tissue-engineered model	[31]
Bone/GTR application	Retained fish-scale collagen–HAp membrane (WM)	BMSCs; Bio-Gide® comparator	Cytocompatibility; osteogenic differentiation (E2)	Whole-scale collagen–mineral matrix	[33]
Periodontal regeneration	Grass-carp collagen/chitosan + HAp membrane (CC)	Cell studies + rat periodontal defects	Osteogenic differentiation; periodontal bone regeneration (E4)	Effect reflects collagen + chitosan + HAp	[34]

Corneal scaffold	Processed fish-scale collagenous matrix (WM)	Optical testing + rat implantation	Encouraging transmission; response depended on placement (E4)	Haze/ inflammation in some conditions	[37]
Corneal substitute	Tilapia-scale matrix (WM)	Rabbit stromal-pocket implantation	Transparency; structural integration (E4)	Protected stromal-pocket model	[38]
Temporary corneal patch	Tilapia BioCornea (WM)	Mini-pig full-thickness perforation	Maintained anterior chamber; sealed perforation short term (E4)	Temporary sealing only	[40]
Endothelial keratoplasty carrier	Cell-seeded fish-scale collagen membrane (WM)	Corneal endothelial cells + rabbit anterior chamber	Supported endothelial-cell construct and implantation (E4)	No human transplantation evidence	[42]

Notes: PC, purified collagen; CC, collagen-containing composite; WM, retained whole-scale collagenous matrix; HAp, hydroxyapatite. E2, cell-based; E3, ex vivo/tissue-engineered; E4, animal/preclinical. Outcomes from composite materials should be attributed to the complete engineered system unless component-control experiments demonstrate a specific collagen effect.

3.6. Evidence, Safety, Standardization, and Translational Limitations

3.6.1. Raw-Material Heterogeneity and Source Control

Fish scales vary among species in structure, mineralization, collagen composition, and physicochemical behavior, and further variation can arise from handling and storage. Translational work therefore requires traceable source information and assessment of batch-to-batch consistency in yield, purity, structure, and critical functional properties.

3.6.2. Inconsistent Extraction and Characterization

Extraction studies are difficult to compare because starting materials, pretreatments, collagen fractions, and yield calculations are not standardized. Ranking methods by percentage yield alone can therefore be misleading.

Meaningful comparison should integrate recovery with identity, purity, structural integrity, thermal behavior, molecular characteristics, and application-relevant function. Standardized analytical panels are preferable because no single method, including SDS-PAGE, FTIR, circular dichroism, thermal analysis, solubility, or fibrillogenesis, establishes functional equivalence by itself.

3.6.3. Biological Safety, Immunological Response, and Allergenicity

Favorable cytocompatibility or a negative acute-toxicity result is not equivalent to universal safety. Biological response depends on source, purification, molecular form, processing residuals, route and duration of exposure, degradation, and the configuration of the final product.

Fish collagen also cannot be assumed to be universally non-allergenic. Kalic *et al*. [44] detected IgE sensitization to purified fish collagen in a subset of 101 fish-allergic patients. Because the tested collagen was derived mainly from fish muscle and skin rather than scales, these findings do not quantify fish-scale risk but show that fish origin does not eliminate collagen-specific allergic responses.

Scale-specific allergenicity remains poorly characterized. Safety assessment should therefore address the final material and, where relevant, microbial quality, endotoxin, residual processing chemicals, cross-linkers, and degradation products, especially for repeated exposure or implantation.

3.6.4. Cross-Linking and Composite Attribution

Material engineering can compensate for some limitations of native collagen. Cross-linking may improve thermal or mechanical stability, while chitosan, alginate, hydroxyapatite, antimicrobial peptides, synthetic polymers, and other additives can provide functions that collagen alone does not offer.

These modifications also complicate attribution. Antibacterial or osteogenic outcomes from multi-component systems cannot be assigned to collagen alone, and greater cross-linking may alter degradation, cell-binding accessibility, or residual chemistry. The PC-CP-CC-WM classification used here is therefore intended to distinguish intrinsic collagen properties from engineered-system performance.

3.6.5. Evidence-Level Imbalance

For descriptive purposes, this review uses an evidence continuum from material characterization (E0) to established practical use (E7). The categories describe experimental maturity rather than methodological quality; a weak animal study is not automatically more informative than a rigorous cell-based study.

Evidence maturity also varies by application. Biomedical studies are still concentrated at the cell and animal levels, with wound healing having the broadest preclinical base, whereas controlled human studies are concentrated in orally administered skin-related collagen peptide products.

3.6.6. Sterilization, Storage, Degradation, and Manufacturing

Biomedical translation involves more than extraction. Sterilization, storage, drying, cross-linking, packaging, and manufacturing can all alter collagen structure, mechanical behavior, swelling, degradation, and biological performance [45].

Sterilization should therefore be validated on the final intended material, and degradation should be matched to application needs. Scale-up also requires defined critical process parameters and quality attributes because laboratory procedures involving prolonged EDTA treatment, repeated washing, dialysis, freeze-drying, or manual fabrication may be difficult to reproduce industrially.

3.6.7. Regulatory and Application-Specific Translation

Regulatory requirements are application-specific: a topical cosmetic, oral peptide product, wound dressing, periodontal membrane, and corneal scaffold follow different evidence and risk pathways.

For medical devices, ISO 10993-1:2025 places biological safety within a risk-management framework, while U.S. Food and Drug Administration guidance emphasizes assessment of the final finished device, including effects of manufacturing, sterilization, and processing residuals. Cytocompatibility of purified collagen therefore cannot be transferred automatically to a modified or sterilized finished product.

Claim boundaries also matter for cosmetics. Under the U.S. Food and Drug Administration framework, appearance-related claims differ from claims intended to affect body structure or function or treat disease; in vitro fibroblast or procollagen responses should therefore not be translated directly into equivalent marketing claims.

The central translational gap is therefore the lack of a continuous evidence chain linking a traceable source and reproducible process to a defined material, final-product safety, application-specific efficacy, and scalable manufacturing (Table 4).

Table 4. Translational Limitations and Research Priorities for Fish-Scale-Derived Collagen.

Issue	Current limitation / implication	Priority for future research
Raw-material variability	Species, architecture, mineralization, and processing history vary; batch properties may differ	Traceable source specifications; multi-batch validation
Process and reporting st andardization	Yield bases and analytical panels differ, limiting comparison of recovery and functionality	Harmonized yield/purity reporting plus minimum structural/ functional characterization
Material form and performance	PC, CP, CC, and WM are often grouped despite different me chanisms; thermal/mechanical properties also vary	Explicit material classification and application-specific performance testing
Composite attribution	Polymers, HAp, antimicrobials, and other agents contribute to outcomes	Component-control studies
Safety and allergenicity	Scale-specific long-term, sensitization, and final-product safe ty data remain limited	Product-specific biological safety and allergenicity evaluation
Sterilization and manufacturing	Sterilization, storage, long demineralization, washing, dialysis, and drying can alter properties or hinder scale-up	Post-sterilization/stability testing; process validation; critical qua lity attributes
Topical human evidence	Controlled topical trials remain scarce	Vehicle-/placebo-controlled human studies with characterized formulations

Biomedical translation	Evidence remains mainly E2–E4; preclinical efficacy is not clinical efficacy	Clinically relevant models and controlled human investigation
Environmental/ economic performance	By-product origin does not establish environmental superiority	Comparative LCA and techno-economic analysis

Note: PC, purified collagen; CP, collagen peptides/hydrolysates; CC, collagen-containing composite; WM, whole-scale collagenous matrix; HAp, hydroxyapatite; LCA, life-cycle assessment.

3.7. Research Gaps and Future Directions

Future work should focus less on expanding the list of possible applications and more on improving comparability, reproducibility, and translation.

Raw-material studies should use traceable, multi-batch characterization, while extraction studies should compare competing methods on the same material using common yield calculations and structural criteria. Recovery, purity, molecular integrity, thermal behavior, and application-relevant function should be evaluated together.

Safety studies should increasingly assess the final product, including scale-specific allergenicity, sensitization, inflammatory responses, residual processing chemicals, degradation products, and the effects of sterilization.

Application-specific models also need to become more demanding. Wound studies require stronger replication and clinically relevant comparators; bone and periodontal studies should separate collagen effects from those of polymers and minerals; and corneal research needs longer-term evaluation and standardized optical testing.

Topical and oral skin applications should continue to be assessed separately. Oral peptide studies would benefit from independent replication across standardized preparations, whereas topical development requires stronger vehicle-controlled human trials supported by molecular characterization and objective skin measurements.

Environmental and economic performance should be measured rather than inferred from by-product origin. Comparative life-cycle and techno-economic studies should account for demineralization chemicals, water and energy use, purification, reagent recovery, wastewater treatment, scale-up efficiency, and the value of mineral co-products [46].

4. CONCLUSIONS

Fish scales are a technically viable source of predominantly type I collagen, but the products obtained from them are not a single material category. Species, scale structure, demineralization, extraction, hydrolysis, and subsequent modification determine whether the final product behaves as purified collagen, a peptide preparation, a composite, or a retained collagenous matrix.

The strongest current evidence supports fish-scale-derived collagen as a developing biomaterial platform rather than an established therapeutic material. Wound healing has the broadest preclinical biomedical evidence, while oral, periodontal, and corneal applications also show substantial experimental development. In several of these areas, however, the best outcomes come from engineered composites or preserved whole-scale matrices rather than purified collagen alone. For skin-related use, controlled human evidence is stronger for oral collagen peptides than for topical application.

Broader use is still limited by inconsistent raw-material and extraction reporting, incomplete product-specific safety assessment, difficulty attributing outcomes in composite systems, manufacturing and sterilization requirements, and limited human biomedical evidence. Environmental sustainability also needs direct evaluation rather than assumption from by-product origin.

Translation should therefore be tailored to the intended application. Oral and topical peptide products require route-specific evidence, whereas implantable collagen materials and collagenous matrices need more extensive characterization, sterilization validation, biocompatibility testing, and preclinical-to-clinical evaluation before they can be compared reliably with established alternatives.

AUTHOR CONTRIBUTIONS

Conceptualization, Y.A. and R.I.P.; methodology, Y.A. and R.I.P.; investigation, Y.A. and R.I.P.; data curation, Y.A. and R.I.P.; writing—original draft preparation, Y.A. and R.I.P.; writing-review and editing, Y.A. and R.I.P.; supervision, Y.A.; project administration, Y.A. All authors have read and approved the final manuscript.

AI DISCLOSURE STATEMENT

During preparation of this manuscript, the authors used ChatGPT (GPT-5.6 Sol, OpenAI) to assist with literature organization, manuscript drafting and restructuring, language editing, and reference-verification support. The authors independently reviewed and verified all scientific interpretations, factual statements, citations, and references, and take full responsibility for the final content. No AI-generated figure is included in the submitted manuscript, and the AI tool was not used to fabricate or manipulate research data.

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