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Review

Scaling the blue gold: process challenges and scale-up constraints in fish skin-derived collagen bioproducts

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ABSTRACT

Collagen is a widely studied biomacromolecule valued for its biocompatibility, low cytotoxicity, and high water-binding capacity, enabling its use across food, cosmetic, nutraceutical, and biomedical sectors. Fish processing by-products, such as skin and scales, offer a rich and sustainable source of collagen type I, providing an eco-friendly alternative to land-based sources. Marine derived collagen is favored for its lower zoonotic risks, minimal ethical and religious barriers, and high acceptability in biomedical applications. Despite numerous successful laboratory studies and the abundant availability of fish processing by-products, current marine collagen extraction methods remain impractical at commercial scale. This review explores the transition from lab to industrial scale extraction, highlighting critical drawbacks such as excessive water and salt requirements and the need for continuous low temperature operations. We also examine often neglected issues, particularly unquantified collagen losses during processing. Emerging strategies such as whole biomass valorization that utilizes both skins and scales, alongside innovative techniques are assessed as scalable and eco-efficient alternatives. Collectively, these insights outline a roadmap for developing cost-effective, sustainable, and industrially feasible systems for extracting collagen from fishery by-products.

1. Introduction

1.1. Food waste

Circular economy, focusing on waste minimization, product lifespan extension, and material reuse, offers a sustainable alternative to the traditional take-make-dispose model and can help tackle both food loss and food waste in food industry (Oliveira et al., 2021). Food loss occurs throughout production, storage, processing, and distribution due to inadequate infrastructure, pests, spoilage, and transportation issues (Cederberg and Sonesson, 2011). Food waste is a significant problem in many developed countries and contributes to environmental degradation, as the discarded food decomposes in landfills, producing greenhouse gases (Vilariño et al., 2017). It is estimated that one-third of all food produced for human consumption is lost or wasted globally (Gustavsson, n.d). The Food Loss Index (FLI) from the Food and Agriculture Organization (FAO) suggests that around 14% of all food produced is lost after harvesting and before reaching retail (The State of Food and Agriculture Innovation in family farming, n.d). According to Eurostat (2022), 69% of food waste in the EU arises from household, food service, and retail sources (Food Waste and Food Waste Prevention-Estimates Statistics Explained, n.d.). A summary paper by the National Resources Defense Council recommends minimizing food waste through improved product development, storage, shopping/ordering, marketing, labeling, and cooking practices, while recycling food waste and valorizing biomass are highlighted as effective strategies for sustainable management (Food Waste | The Nutrition Source | Harvard T.H. Chan School of Public Health, n.d.; Reduce Wasted Food By Feeding Hungry People | US EPA, n.d).

1.2. Fish waste

Rising demand for high–quality protein has placed marine resources in the spotlight, with global fish production reaching 179 million tons in 2018 and projected to increase to 194 million tons by 2026 (Ganjeh et al., 2023; Khan et al., 2020). Fresh, live, or chilled fish account for 44% of direct human consumption, followed by frozen (35%), preserved (11%), and dried, salted, fermented, or smoked products (10%). However, fish processing generates 30–70% waste, depending on the species, resulting in over 28 million tons of by-products annually, including

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heads, viscera, blood, and skin (Food Waste Index Report, 2021). In the past, fish by-products were commonly discarded as waste, used as animal feed, or utilized in silage and fertilizers (Ganjeh et al., 2023). More recently, fish by-products have gained attention for alternative applications, as they represent a rich nutritional resource, providing proteins, bioactive peptides, lipids, hydroxyapatite, essential fatty acids, and more, and can be valorized across a wide variety of applications(Fig. 1) (Food Waste Index Report, 2021; Ganjeh et al., 2023).

1.3. Marine sourced collagen

Collagen is a key structural protein in animal connective tissues whose biocompatibility, biodegradability, and low immunogenicity make it ideal for pharmaceutical, food, and cosmetic applications (Issains et al., 2019). In most animals, collagen makes up about 30% of the total body protein weight, making it the most prevalent protein (Bisht et al., 2021). Collagen's complex supramolecular architecture varies across tissues, supporting a wide range of biological functions, yet religious and cultural restrictions have limited the use of mammalian-derived collagen (Espinales et al., 2023). However, collagen sourced from marine organisms provides a disease-safe and, in most cases, ethically acceptable substitute for land-based sourced collagen (Jafari et al., 2020). The European Commission's implementation of the "Blue Growth" strategy underscores the need for the sustainable use of marine resources and environmental protection. With seafood processing generating millions of tons of by-products, over half of each fish's weight in fins, heads, skin, and viscera these represent a vast, underexploited reservoir of valuable biomolecules (Maschmeyer et al., 2020; Rajabimashhadi et al., 2023). As global fish production surges to meet Sustainable Development Agenda 2030 targets, the resulting seafood processing waste poses significant environmental, public health, and economic challenges (Rajabimashhadi et al., 2023). Some fish processing by-products are still landfilled or destroyed, yet these wastes contain valuable compounds such as oils, proteins, pigments, bioactive peptides and amino acids. The recovery of these compounds could reduce disposal costs and unlock significant economic value (Silvipriya et al., 2015). The exploration of fish by-products as an innovative source of collagen has garnered considerable attention due to their high protein content, negligible risks of disease transmission, significant bioactivity, and minimal religious and ethical constraints (Rajabimashhadi et al., 2023). For many religions, fish is generally permissible, therefore marine collagen can be certified halal or kosher if processed properly. According to the Islamic law, certain fish such as cod, salmon, and tilapia are considered halal, while under Jewish dietary law, only fish with fins and scales are regarded as kosher. Thus, collagen derived from these species can be certified as halal or kosher, provided that additional requirements are met, including low heavy metal levels (<10–20 ppm), absence of antibiotics, and chlorine content below 10 ppm (Duasa et al., 2022).

Fish skin, traditionally treated as waste, offers a rich and underutilized source of high-quality type I collagen, chemically like human skin. Abundant and biocompatible, collagen obtained from different fish species is increasingly favored for biomedical, cosmetic, and nutraceutical applications (Farooq et al., 2024a; Song et al., 2021). Marine collagen products, however, fall under different regulatory frameworks by end-use. For instance, in the EU, collagen or hydrolyzed collagen is a cosmetic ingredient under Regulation 1223/2009; cGMP (ISO 22716), under safe concentrations, although companies must ensure microbial safety, correct labelling, and consistent with cosmetic claims rules (Dondero et al., 2025).

1.4. Chemical and molecular structure of collagen type I

Collagen plays a central role in forming the extracellular matrix, a complex scaffold produced by fibroblasts and other cells that provide structural support and regulates cellular behaviour (Rodrigues et al., 2023). Fish skin contains low-molecular-weight collagen that is easily absorbed and highly bioavailable, exhibiting strong water-binding capacity and contributing to improved skin hydration and a more youthful appearance (Chandrasekaran et al., 2024). Its high content of glycine, proline, and hydroxyproline further stimulates endogenous collagen synthesis, thereby supporting tissue repair and regeneration (Coppola et al., 2020). Researchers have identified 28 collagen types, all sharing the triple-helix motif but differing in subtle structural features that confer specialized functions throughout the body (Coppola et al., 2020; Fatiroi et al., 2023). Type I collagen is the most abundant collagen in the human body, accounting for over 90% of total collagen content. It comprises three α chains, consisting of two α1 chains and one α2 chain, that assemble into the characteristic triple-helix structure (Matarsim et al., 2023). Collagen is characterized by its α-chains, which feature a repeating tripeptide sequence (Gly-X-Y), where glycine (Gly) is invariably present, typically accompanied by proline (Pro) and hydroxyproline (Hyp), forming the collagen-specific Gly-Pro-Hyp motif (Bisht et al., 2021). These α-chains can form covalent and water-mediated hydrogen bonds, assembling into higher-order structures: dimers and trimers of α-chains, characterized by high molecular weight, and known as β and γ

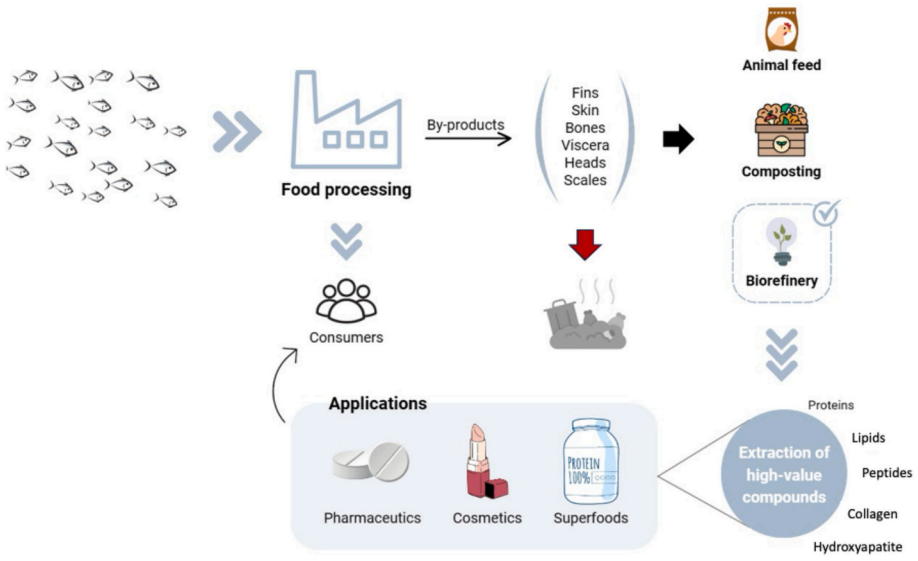

Fig. 1. Applications of fish waste as a valuable biomass containing commercially relevant biomolecules.

components, respectively(Fatiroi et al., 2023; Grefstad, 2022). Therefore, Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) is commonly used to assess both the purity and molecular weight of collagen extracted from fish skins (Bisht et al., 2021). Typically, α1 and α2 chains present molecular weights ranging from 100 kDa to 130 kDa, while β- and γ-chains (dimers and trimers of α-chains) exhibit higher molecular weights exceeding 240 kDa (Grefstad, 2022; Rodrigues et al., 2023). Studies indicate that most collagen found in fish is comprised of a β-chain and two α-chains (α1 and α2, with α2 at a slightly lower molecular weight), confirming the predominance of collagen type I (Atef et al., 2020; Matarsim et al., 2023). The structural integrity of collagen can be confirmed using Fourier Transform Infrared (FTIR) spectroscopy, by the main absorption bands for amides A, B, I, II, and III near 3290, 3080, 1630, 1535, and 1240 cm^{-1}, respectively (Riaz et al., 2018). Collagen secondary structure is usually assessed using Circular Dichroism (CD) spectroscopy, where a notable peak ranging from positive 222 to 220 nm means the presence of a triple helix, while a corresponding dip between negative 200 and 196 nm characterizes the random coil configuration (Bisht et al., 2021).

1.5. Biomedical, cosmetic and nutraceutical applications of marine collagen derivatives

Tissue regeneration and marine collagen applications hinge on selecting the right collagen type and source to ensure proper tissue function, strength, and structural integrity (Furtado et al., 2022). Collagen is a key scaffold material for osteogenesis and bone tissue engineering and marine collagen has shown particularly promising potential, enhancing bone mineral density, promoting osteoblast maturation and proliferation, and contributing to the treatment of osteoporosis and osteoarthritis (Bourdon et al., 2021). As a material (for scaffolds and wound dressings), fish collagen must meet medical or pharmaceutical standards (ISO 10,993 biocompatibility, endotoxin limits, etc.) (Rajabimashhadi et al., 2023).

Collagen pro–angiogenic properties, along with its ability to promote keratinocyte and fibroblast migration, have been shown to accelerate wound healing and mitigate skin aging (Geahchan et al., 2022). In regenerative medicine, marine collagen stands out as a versatile material: it supports chondrogenic differentiation for cartilage repair, preserves stem-cell multipotency, and shows great promise for applications in bone and corneal regeneration (Hsu et al., 2016). These attributes position marine collagen as a key scaffold component for tissue engineering and stem–cell–based therapies (Bourdon et al., 2021; Liu, 2021). Collagen–based dermal fillers, administered via subcutaneous injection, improve skin quality and density by supporting tissue repair. In the nutraceutical sector, orally delivered collagen hydrolysates provide bioactive peptides that chemotactically stimulate fibroblasts, promoting skin regeneration and repair (Lupu et al., 2019). Owing to its superior water–binding capacity, marine collagen also serves as an excellent humectant and film–forming agent in cosmetics, helping to maintain skin hydration, reduce trans–epidermal water loss, and improve skin softness (Lupu et al., 2019; Muzumdar and Ferenczi, 2021; Sionkowska et al., 2020).

Nile tilapia skin has emerged as a promising collagen–based alternative to traditional skin grafts for burn treatment. Preclinical studies show that tilapia collagen dressings significantly accelerate wound closure and stimulate cell proliferation, demonstrating their potential to enhance tissue regeneration and healing (Elbialy et al., 2020; Geahchan et al., 2022). Marine type I collagen is currently being developed in multiple formats, including peptides from Nile tilapia, oligopeptides from salmon skin, and extracts from tuna skin and scales, as well as non–fish sources like the sponge *Chondrosia reniformis*, whose collagen exhibits favorable rheological and adhesive properties (Rahman and Silva, 2022). Furthermore, combining cryopreserved stromal vascular fractions with marine collagen has shown promise in promoting vascularization in engineered tissues (Freitas-Ribeiro et al., 2022). In vivo preclinical studies report benefits across multiple parameters, such as glycemic control, inflammation reduction, and tissue repair, supporting the potential of marine collagen in wound healing, bone regeneration, and the development of scaffolds for skin, dental, cartilage, and nerve repair (Feng et al., 2023; Xu et al., 2021). Commercially, several marine collagen-based products are already available. Examples include Solgar, a collagen-hyaluronic acid supplement; Vital Proteins, a set of hydrolyzed collagen supplements for hair, nails, skin, and joint health; Oceancoll, which combines collagen type I with vitamin C to support healthy joints, bone, skin, hair, and muscles; and MyProtein, a highly purified hydrolyzed collagen peptide supplement marketed for fitness, weight management and muscle mass gain (Ácido Hialurónico e Colagénio – Solgar Portugal, n.d; Collagen Protein | Protein Supplements | MYPROTEIN, n.d; Hydrolyzed Marine Collagen - Oceancoll, n.d).

1.6. Review background

While several high-quality reviews have comprehensively summarized marine collagen sources, extraction methodologies, structural characterization, and application domains (Farooq et al., 2024b; Gutierrez-Canul et al., 2025), the present work advances a different perspective centred on translational relevance. This review provides a process-oriented and sustainability-informed synthesis of fish skin collagen production, integrating technical performance with industrial feasibility considerations. Rather than focusing solely on collagen structural preservation, the manuscript evaluates process design, operational efficiency, and resource intensity across reported methodologies. It systematically examines pretreatment strategies, solid-to-liquid ratios, water consumption associated with sequential washing and purification steps, temperature-dependent extraction regimes, recovery strategies based on salt precipitation, collagen losses across processing fractions, and cumulative energy demand.

1.7. Literature search strategy

To ensure transparency in the literature selection, a structured search strategy was adopted. Relevant publications were identified through major scientific databases (e.g., Google Scholar and ISI Web of Knowledge) using combinations of keywords including “fish skin collagen extraction,” “marine collagen extraction,” “acid-soluble collagen,” “pepsin-soluble collagen,” and “marine by-product valorization.” The review primarily focuses on peer-reviewed studies reporting collagen extraction from fish skin, while selected marine collagen studies from other tissues were included when they provided relevant process or methodological insights. No strict temporal restriction was applied; however, emphasis was placed on studies published in the last decade to capture both conventional extraction approaches and emerging process-intensification techniques. Studies were considered when they reported quantitative process parameters such as extraction yield, solvent systems, solid-to-liquid ratios, or processing time, enabling a comparative evaluation of operational performance. By contextualizing these parameters within realistic production scenarios, this review provides a more comprehensive information of process performance and technological readiness. Through this integrated analysis, the work identifies critical leverage points for improving efficiency, reducing environmental burden, and enhancing economic viability. The resulting framework supports the rational development of scalable, resource-efficient collagen extraction platforms, contributing to the advancement of fish skin collagen from laboratory validation toward industrial setup.

2. Collagen extraction process

2.1. Overview

To extract collagen from fish skins, a multi-step process is carried out

Fig. 2. Schematic diagram representing the multi-step process normally applied to extract collagen from fish skins.

(Fig. 2). Briefly, the skins are cleaned to remove contaminants, followed by a demineralization process that removes minerals to enhance the purity of the collagen obtained. Then, enzymatic, salt, and acidic treatments alone or combined are applied to break down the connective structure and inter-intramolecular interactions, with or without enhancements such as ultrasonication, to facilitate the release of collagen fibers (Rajabimashhadi et al., 2023).

The extracted collagen is finally purified, dried, and processed into various forms, such as powders, gels, or sheets, depending on its intended use (Muhammad et al., 2017).

Before the collagen extraction procedure, some information should be available, such as the marine type, the origin of the marine biomass, and the storage temperature (Table 1). Considering the wide variety of collagen extraction methodologies, various factors before the extraction process can directly affect collagen purity, yield and bioactivity. These include biomass storage conditions and transportation parameters, which may significantly affect the integrity of the starting material (Muhammad et al., 2017). Reporting such information can be valuable because it allows researchers to assess potential correlations between pre-extraction handling, collagen purity and quality, and the yield, beyond the effects of the extraction materials and methods.

2.2. Pretreatment

For the fish skin pretreatment, three main steps are involved: skin cleaning, removal of non-collagenous proteins, and defatting to eliminate lipids and other unwanted biocomponents (Bisht et al., 2021). Residual tissues, such as muscle fragments or adhering fat, must first be removed to minimize impurities that could compromise the yield and quality of the final collagen product. Non-collagenous proteins are commonly removed using a 0.1 M sodium hydroxide (NaOH) solution with a 1:10 (w/v) solid to solvent ratio (SSR) for 24–48 h, with the NaOH solution changed every 6 h. Defatting can be accomplished by employing a solution of 10% (v/v) of butyl alcohol (or other solvents like ethanol) at the same 1:10 (w/v) solid to solvent ratio for 48 h, with solvent replacement every 6 h (Arumugam et al., 2018). Alcohols (such as butanol or ethanol), acetone, sodium hydroxide (NaOH), and hydrogen peroxide are the solvents commonly used to remove impurities such as non–collagenous proteins, lipids, and pigments from fish skin. Alternatively, moderate concentrations of sodium chloride (NaCl) can be used as a milder option for deproteinization (Tian et al., 2021). These mild purification steps selectively remove impurities while preserving the integrity of collagen. However, dilute alkali solutions can partially hydrolyze collagen cross–links. Therefore, a careful control of solvent concentration and exposure time is essential to minimize collagen losses (Coscueta et al., 2021). NaOH, however, is highly effective because it not only removes non-collagenous proteins but converts fats into soap-like compounds that are easily removed. Typically, NaOH concentrations for effective fat removal range from 0.1 to 0.15 M (Bisht et al., 2021; Matinong et al., 2022).

Temperature is also crucial in both fat removal and collagen extraction. While higher temperatures can increase fat solubility and improve removal efficiency, excessively high temperatures may result in the collagen denaturation or partial degradation (Olatunji and Denloye, 2017). Hence, finding the optimal temperature range that effectively removes fat while preserving collagen integrity is essential. For instance, collagen obtained from codfish skin is reported to be sensitive to denaturation above 15 °C, and the pretreatment steps, including fat removal, are usually conducted at around 4 °C to maintain structural stability (Table 1) (Bisht et al., 2021; Carvalho et al., 2018).

2.3. Extraction and purification

The extraction step is very important as it may affects the collagen native triple helical structure, what may have a significant impact for certain biomedical applications (Song et al., 2021). Various approaches have been utilized to optimize the extraction process, such as using organic acids alone or in combination with enzymes, salts, and/or bacteria (Table 1). The commonly employed methods for the collagen extraction are named after the type of extraction method such as acid-soluble collagen (ASC), salt-soluble collagen (SSC), and pepsin-soluble collagen (PSC) (Sun et al., 2017). In ASC extraction, fish skins are treated with weak or inorganic acids such as acetic acid or hydrochloric acid to dissolve the collagen. This method is preferred when intact collagen fibers are required. These acids effectively solubilize collagen, producing high yields and a product with excellent quality (Khiari et al., 2017). However, it is important to consider the choice and concentration of the organic acid used, as they can affect the extraction efficiency and the characteristics of the extracted collagen (Shaik et al., 2021). Various organic acids, including acetic, propionic, lactic, and citric acids have been investigated (Bisht et al., 2021; Matarsim et al., 2023). The results suggest that the application of organic acids for collagen extraction, neat or as one of the starting materials to prepare (Deep) Eutectic Solvents (DES), yields promising results (Bai et al., 2017; Bisht et al., 2021). Studies indicate that collagen extraction can be effectively performed using 0.5 M of acetic acid aqueous solutions, ranging from 0.1 to 0.75 M of acetic acid, with a solid–liquid ratio of 1:10 (w/v) or higher. The resulting viscous solution contains the collagen extracted from the fish skin (Bisht et al., 2021; Tang et al., 2015).

PSC extraction exploits the proteolytic specificity of pepsin to degrade non–collagenous proteins in fish skin, thereby increasing both yield and purity of the collagen fraction (Wei et al., 2019). By selectively cleaving the non–helical telopeptide regions, pepsin liberates intact triple–helical collagen molecules while removing contaminating proteins, and as a result, PSC workflows consistently produce high–purity type I collagen, making them especially suited for demanding biomedical and pharmaceutical applications (Jongjareonrak et al., 2005; Nalinanon et al., 2007). Researchers have been trying to adjust parameters such as acid concentration, enzyme concentration, and extraction conditions to achieve higher yields and purer collagen in its native structure, that would be suitable for a variety of applications (Table 1). SSC extraction uses salt solutions to dissolve the collagen, and by adjusting the salt concentration and pH, collagen can be selectively extracted while leaving behind unwanted components, resulting in hydrolyzed collagen with good mechanical properties and stability (Candlish, 1963).

After the extraction phase, collagen is typically recovered from the solvent through a multi-step purification process consisting of precipitation, dialysis, and freeze-drying (Gaikwad and Kim, 2024). In general, the recovery begins with the addition of sodium chloride to the collagen-containing solution, commonly at a final concentration of about 2.6 M in presence of a neutral buffer (e.g. 0.05 M Tris-HCl at pH 7.4) (Bisht et al., 2021). This high ionic strength promotes the selective precipitation of collagen molecules, particularly those of Type I (Phon et al., 2023). The

Table 1
The type of marine sources, origin, storage condition, and some other specifications of collagen extracted.

Fish type	Biomass	Country	Storage temperature (°C)	Time delay	Extraction method	Precipitation	Process temperature (°C)	Solid to solvent ratio (w/v)	Total yield (wet weight %)	Specification	Ref.
Nile perch (*Lates niloticus*)	By-product of fillet processing Blended skin from different parts	Uganda	7	48 h	ASC	NaCl 0.9	15	1:20	58	Homogenization for 4 days, fragments measuring 0.5 cm in both length and width Ethanol 10% for fats removal, solvent replaced 2x per day Re-dissolved in acetic acid Re-precipitated. A relatively high yield obtained. The collagen extracted from fish skin exhibited higher imino acid content, corresponding to a higher denaturation temperature compared with other fish species reported.	(Muyonga et al., 2004)
Nile tilapia (*Oreochromis niloticus*)	Fish skins as by-products of fillet processing	China	−20	–	ASC PSC	NaCl Molarity NA	4	1:60	4.27 7.6	Combined with fermentation using *Bacillus velezensis FEL-BM21* NaCl concentrations of 0% up to 6% (w/v) in 0.5 M acetic acid. Fermentation is suggested as a viable alternative pretreatment method for collagen extraction materials; however, its contribution to improving extraction yield was not significant.	(Song et al., 2021)
Brownstripe red snapper (*Lutjanus vitta*)	Fresh fish captured Stored under ice	Thailand	Under ice	24 – 36 h	ASC PSC	NaCl 2.6 M in 0.05 M tris-HCl	4	1:30	9 4.7	2 steps of dialysis. Enzymatic process (pepsin) First dialysis with acetic acid 0.1 M Second dialysis with distilled water 0.1 M. A sharp decline in solubility occurred at NaCl concentrations above 2% and 3% (w/v) for ASC and PSC, respectively. T_{max} value for both collagen fractions decreased in the presence of acetic acid, indicating acid-induced structural alterations.	(Jongjareonrak et al., 2005)
Brownbanded bamboo shark (BBS) (*Chiloscyllium punctatum*) Blacktip shark (*Carcharhinus limbatus*) (BTS) Cartilages	Cartilages provided by Blue Ocean Food Products Co., Ltd.	Thailand	Stored under ice at −20	Under 2 months	ASC PSC	NaCl 2.6 in presence of Tris 0.05 M	4	1:10 1:15	1.27 9.59 g/100 g	Defrosted by tap water until the core temperature reached 5 °C Cleaned by washing with cold tap water (<10 °C). The pellet dissolved in a solution containing acetic acid 0.5 mol.L^{-1}. First dialysis with acetic acid solution for 12 h. Second dialysis against distilled water for 48 h. Porcine pepsin was added to the solution. All collagen samples contained trace levels of ash and fat. The results indicated that pepsin hydrolysis did not significantly affect the collagen secondary structure, particularly the triple-helical conformation.	(Kittiphattanabawon et al., 2010)

(*continued on next page*)

Table 1 (*continued*)

Fish type	Biomass	Country	Storage temperature (°C)	Time delay	Extraction method	Precipitation	Process temperature (°C)	Solid to solvent ratio (w/v)	Total yield (wet weight %)	Specification	Ref.
Yellow-fin tuna (*Thunnus albacares*) bladder and stomach	Swim bladders and stomach of yellowfin tuna obtained from Songkla Canning Public Co., Ltd.	Thailand	Carried Under ice Stored at −20	Under 3 months	ASC PSC	NaCl 2.6 in the presence of 0.05 M tris (hydroxymethyl) aminomethane at pH 7.5	Entirely at 4 °C	1:10	1.07 12.10	Defrosted with water, at 26 to 28 °C Samples grounded in liquid nitrogen Mixed stomach powder with 20 mM sodium phosphate buffer (pH 7.0) containing 1 mM phenylmethylsulfonyl fluoride (1:5 (w/v)) Stirring at 4 °C for 3 h Proteolytic activity prior to the ASC and PSC extraction First dialysis against acetic acid 0.1 M Second dialysis against distilled water 5x. Acid-soluble collagen exhibited lower yield and imino acid content than pepsin-soluble collagen.	(Kaewdang et al., 2014)
Spanish mackerel (*Scomberomorous niphonius*), skin (S) and bone (B)	Fresh skin and bone purchased from Nanzhen market	China	Carried Under ice Stored at −20	Within 60 mins	ASC-S PSC-S ASC-B PSC-B	NaCl 2.6 at the presence of 0.05 M tris (hydroxymethyl) aminomethane at pH 7.5	Entirely at 4 °C	1:10 1:15	13.68 3.49 12.54 14.27	Five days of biomass pretreatment PSC extraction took place after ASC extraction First dialysis against acetic acid 0.1 M for 48 h Second dialysis against distilled water for 48 h. PSCs exhibited lower levels of high-molecular-weight cross-links than ASCs. Collagen samples obtained by both methods showed denaturation temperatures below 20 °C, attributed to low imino acid content.	(Li et al., 2013)
Paper nautilus (*Argonauta argo*)	Paper nautilus outer skin Freshly caught from Hibiki Nada Sea	Japan	Stored at −85	–	ASC PSC	Salting out at NaCl 0.7 M Final concentration 2.3 M in the presence of 0.05 M Tris-HCl at pH 7.5	Entirely at 4 °C	NA	5.2 50	Protein digestion (pepsin 10% (w/v)) at 4 °C for 2 days Pepsin inactivation against 0.02 M Na_2HPO_4 (pH 7.2) for 72 h Change of solution once a day Re-extraction procedure was done First dialysis against 0.1 M of acetic acid. Second dialysis against distilled water. To improve utilization of limited resources, collagen was extracted from the outer skin of the paper nautilus; however, poor solubilization in 0.5 M acetic acid resulted in low yield.	(Nagai and Suzuki, n. d.)
Amur sturgeon (*Acipenser schrenckii*)	Biomass were provided by company	China	Stored at −20	–	SSC ASC PSC	NaCl 0.45 NaCl 0.9 0.1% (w/v) in 0.01 M HCl	Entirely at 4 °C	1:100	4.55 37.42 52.80	Biomass exposed to pepsin extraction in HCl. Non-collagenous substances removal by homogenizing in 20% (w/v) NaCl (1:20), 3x. SEM analysis revealed that the collagen samples formed dense, sheet-like films interconnected by random-coiled filaments. Collagen denaturation temperatures were higher than those typically reported for	(Wang et al., 2014)

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Table 1 (*continued*)

Fish type	Biomass	Country	Storage temperature (°C)	Time delay	Extraction method	Precipitation	Process temperature (°C)	Solid to solvent ratio (w/v)	Total yield (wet weight %)	Specification	Ref.
										marine collagen. FTIR indicated stronger hydrogen bonding within the triple-helical structure of PSC and more intermolecular crosslinks in ASC, suggesting that collagen from Amur sturgeon skin could serve as an alternative to mammalian collagen.	

mixture is then incubated at 4 °C for 12–24 h to allow complete sedimentation (Bisht et al., 2021). Following incubation, the precipitated collagen is collected by centrifugation, typically at ≥4500 rpm for up to 120 min, generally at 4 °C (Bisht et al., 2021; Jafari et al., 2020). The resulting pellet, containing crude collagen, is then either resuspended in a minimal volume of diluted acid (acetic acid with molarity depending on the protocol) to solubilize the collagen, while leaving non-collagenous contaminants insoluble, or directly dialyzed against distilled water to remove the salt (Farooq et al., 2024a). Dialysis is performed using membranes with a molecular weight cut-off of 3–14 kDa against cold distilled water or dilute acetic acid for 48–72 h. The dialysis solution is refreshed up to 5 times per day to ensure effective removal of NaCl and acid residues. Proper dialysis is crucial, as residual salts can compromise the downstream processing performance and reduce the stability of the final collagen (Coppola et al., 2020; Laasri et al., 2023). After dialysis, the purified collagen solution is typically frozen at −80 °C overnight prior to lyophilization. Freeze-drying under reduced pressure removes water, resulting in a porous, dry collagen product that preserves its biochemical and structural properties. The lyophilized collagen can then be stored at −20 °C or below for future analysis (Bisht et al., 2021). This conventional sequence, NaCl precipitation, dialysis, and freeze-drying, remains a foundational approach for isolating collagen from marine sources, ensuring both structural integrity and product purity (Farooq et al., 2024a; Gaikwad and Kim, 2024).

3. Discussion and future trends

3.1. Fish skin collagen extraction: Practical drawbacks

In the lab, collagen extraction from fish skin typically involves extensive manual pretreatment such as removing scales and residual flesh by hand or simple cutters, long biomass soaking in water with frequent water changes, and size reduction to increase surface area for chemical treatments (Bisht et al., 2021; Chandrasekaran et al., 2024). While effective for research, these steps are impractical at industrial throughput, labor-intensive, and time-consuming (Ideia et al., 2019). For industrial processes the basic lab workflow must be adapted and combined with continuous, automated unit operations and intensive schemes. Key process improvements include using the whole biomass (including scales, which represent 5–10% of the total collagen content), applying controlled size reduction with industrial grinders or coarse mills to reach the target particle size, minimizing washing steps to remove salt and contaminants, replacing slow dialysis with membrane-based techniques (ultra/nano filtration) for desalting, and implementing solvent recycling. These changes will reduce operating costs and improve workflow (Gaikwad and Kim, 2024; Kuwahara, 2021). Adopting these industrial procedures preserves the lab-proven chemistry while solving scale bottlenecks by increasing the throughput, maximizing total collagen yield, reducing energy and material use *per* kg of product, therefore enabling continuous operation with consistent quality control suitable for supply chains.

Collagen is most recovered by salting-out (Bisht et al., 2021; Cadar et al., 2024). The addition of NaCl to approximately 2.6 M causes precipitation of collagen from the acidic extract (Farooq et al., 2024a; Rajabimashhadi et al., 2023). NaCl is widely used due to its low cost and the ease with which the precipitate can be collected by centrifugation. The pellet is then either redissolved in a smaller volume of diluted acid (commonly acetic acid) for further purification or subjected directly to dialysis to remove residual salt (Farooq et al., 2024a). Following precipitation with ~2.6 M NaCl (≈15.2 g per 100 mL solvent), dialysis typically proceeds for 24–48 h, with distilled water changed every 6 to 12 h (Bisht et al., 2021; Chen et al., 2016a; Kuwahara, 2021; O'Sullivan et al., 2006). Each 100 mL of extract consumes about 5 L of water *per* exchange, amounting to ≥15 L per day for desalting alone. Whether recovery is achieved by salting out or membrane filtration, such protocols are time-consuming, and water intensive, often requiring to 2–10

days to be completed (Farooq et al., 2024a; Matinong et al., 2022). Repeated exposure to high ionic strength, particularly when recovering collagen from salted marine biomass, such as codfish skin, can disrupt telopeptide hydrogen bonding, compromising the integrity of the triple helix. This leads to reduced thermal stability and mechanical performance, yet such degradative effects are rarely quantified in current studies (Belouafa et al., 2018). Moreover, high ionic strength promotes collagen aggregation and, when combined with high temperatures, accelerates its conversion to gelatin. Therefore, residual salts must be effectively removed to avoid solubility problems and adverse effects during downstream processing (Cadar et al., 2024). While sodium salt facilitates collagen precipitation, it introduces significant costs and an environmental burden due to the water required for purification (Farooq et al., 2024a; Saallah et al., 2021; Shen et al., 2009).

Excessive solvent use and impractical solid-solvent ratios (SSR) also increase process costs and environmental footprint, especially as most protocols are designed to deal with biomass quantities below 100 g (Farooq et al., 2024a). Even under optimistic scenarios (≥99% collagen recovery), recovering approximately. 200 g of type I collagen from 1 kg of fish skin requires approximately 12–15 m^3 of water for dialysis alone (Blanco et al., 2019; Gaikwad and Kim, 2024; Laasri et al., 2023). In practice, yields rarely approach this value; most studies report yields below 20% (Table 1), meaning 60–90 m^3 of water are required per gram of collagen recovered (Bisht et al., 2021; Carpio et al., 2023; Chen et al., 2016a; Grefstad, 2022; Kuwahara, 2021).

Fig. 3 shows the collagen extraction yield from various fish skin over 80 h of extraction, highlighting that overall yields remain relatively low even at extended extraction times across the various solvents tested (Arumugam et al., 2018; Gaikwad and Kim, 2024; Jafari et al., 2020). Therefore, current marine collagen extraction methods mostly remain at the laboratory scale or in niche applications, rather than being ready for widespread industrial use deployment.

Harsh pre-treatments (prolonged solvent exposure or high solvent molarity) can damage collagen fibrils and reduce yields (Kurniawan et al., 2024), while aggressive enzymatic or acidic hydrolysis can irreversibly convert collagen to gelatin or peptides that end up in effluent streams rather than as final product (Rajabimashhadi et al., 2023). Additional losses are likely during recovery and purification, as fish collagens have low salt tolerance (>3% NaCl greatly reduces solubility), leaving collagen behind in supernatant or wash waters when precipitation is incomplete (Coscueta et al., 2021). Excessive water consumption not only significantly inflates production costs but also raises serious sustainability concerns. Combined with inadequate pre-treatments, which often generate low–molecular–weight peptides, this results in substantial collagen loss (Kurniawan et al., 2024). These losses are rarely quantified whether due to excessive washing or discarded scales, resulting in overestimated reported yields and concealing critical inefficiencies in the process (Bai et al., 2017; Liu et al., 2025). Many extraction procedures recover only a small fraction of type I collagen available, most being lost in discarded residues or during subsequent steps (Batista et al., 2022; Bisht et al., 2021). Such approaches demand very high water-to-biomass ratios that when combined with the total water required throughout the entire process, result in consumption of hundreds of liters of water *per* gram of skin (Cadar et al., 2024; Farooq et al., 2024a).

Another significant drawback of collagen recovery from fish skin, from cold-water species such as codfish, is the infrastructure required to maintain extraction temperatures near 4 °C. This requires specialized facilities and continuous cooling of large-scale reactors for several days, driving up energy and resource consumption and operating costs. For some specific types of biomass waste such as semi-dried salted codfish skin, these strict conditions may not be necessary or economically viable considering the value of the end-product. The decision to pursue native collagen, gelatin, or hydrolysates should therefore consider whether the added cost of temperature control is warranted by the quality and market value of the end material.

Even the final drying step introduces risks: high-temperature spray-drying can cause oxidation and peptide bond breakage, while freeze-drying may induce crosslinking or residue oxidation (Zeng et al., 2013). Industrial-scale collagen recovery thus requires a carefully

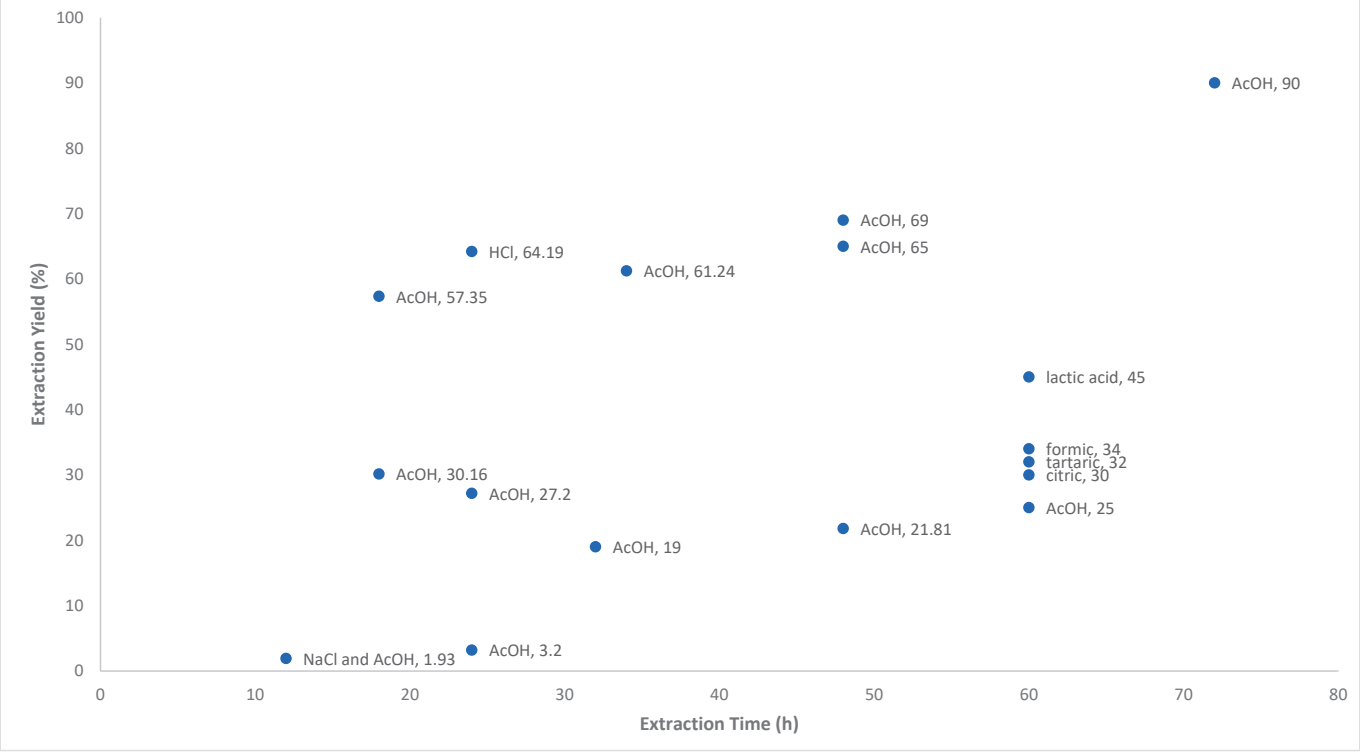

Fig. 3. Collagen extraction yield (%) from fish skin over 80 h using various solvents. AcOH = acetic acid (CH_3COOH). Data points indicate collagen yield (%) at the reported extraction time (hours).

optimized strategy for every step, from pretreatment to drying, to maximize yield and preserve collagen's native structure, if that is indeed the goal (Carpio et al., 2023; Kurniawan et al., 2024). Collectively, these factors (low yields, large SSR, and preservation of the triple helix under low-temperature operation) represent fundamental barriers to the industrial valorization of marine biomass for collagen production, blocking the way for economically viable and environmentally sustainable marine collagen production at industrial scale (Table 1 and Supplementary Table 1) (Arumugam et al., 2018; Bhuimbar et al., 2019; Bisht et al., 2021; Farooq et al., 2024a; Prajaputra et al., 2024).

3.2. Fish skin collagen extraction: Scaling the blue gold by sustainable strategies

To overcome scale-up barriers and move towards sustainable, and integrated strategies, the field is increasingly adopting comprehensive processes (Kurniawan et al., 2024). A key step is whole-biomass processing, where the entire fish skin (including scales and residual flesh) is ground into small (~1–3 mm) particles prior to chemical treatment. This size reduction increases surface area and mass transfer, enabling faster, more uniform extraction, and recover collagen from scales that would otherwise be discarded (Gaikwad and Kim, 2024; Kuwahara, 2021; Liu et al., 2012). Following milling, simple, and environmentally friendly pretreatments, such as NaOH or salt washes, can be adopted. Moreover, the integration of low ionic strength, green solvents, such as biodegradable (deep) eutectic mixtures (DES) of cholinium chloride, urea, and organic acids, enables collagen solubilization under controlled temperature and pH conditions (Bai et al., 2017; Bisht et al., 2021). In the subsequent stage, eco-friendly solvents, such as weak organic acids or aqueous DES can be employed under controlled pH conditions to improve collagen solubilization, and instead of conventional salting-out, isoelectric precipitation may be applied by adjusting the extract to collagen's isoelectric point (pH ~5–6), allowing collagen to precipitate without the addition of salt [95]. For context, a study on tuna skin reported isoelectric recovery yields of ~17.2% of collagen (dry weight), compared with ~14.1% achieved via NaCl precipitation (Lin et al., 2019). Although these yields remain below levels required for full commercial viability, they establish a basis for further development aimed at eliminating salt recovery steps, thereby improving scalability sustainability, and costs. Notably, these approaches reduce wastewater generation and eliminate the lengthy dialysis operations traditionally required to remove salt residues from the final product (Carpio et al., 2023; Kurniawan et al., 2024). As highlighted earlier, excessive water consumption across conventional marine collagen extraction workflows not only increases production costs but also undermines sustainability. Typical SSR (up to 1:30 w/v), use about 30 L of solvent per kg of raw material, in addition to water volume needed for other processing steps (close to 11 m^3 of water per tonne of biomass for washing, thawing, etc.), highlights the need to develop more efficient extraction methods (higher collagen yields), and to lower the water consumption and wastewater production (Ghalamara et al., 2024). Downstream processing and final formulation are also major determinants of product quality and process economics. While lyophilization (freeze-drying) is widely used to preserve collagen's structure [86], Life-Cycle Analyses (LCA) confirmed that energy used for drying along with stirring and centrifugation, dominates the environmental impact of the process(Dondero et al., 2025; Rajabimashhadi et al., 2023). However, reported global-warming footprints range widely (0.15–1.18 kg CO_2-eq *per* g of collagen, depending on the process and scale), but key insight is that up to 80% of CO_2-eq comes from energy-intensive lab-scale steps (stirring, freeze-drying). Therefore, new strategies are expected to cut energy and costs dramatically (Dondero et al., 2025). Thai Union scaled up collagen production from tuna skin (marketed as ThalaCol) by investing 30 m USD dedicated to 1500-ton per year processing facility sited near its tuna operations (within approx. 5 km) to integrate raw-material supply and minimize transport and raw-handling costs(Thai Union Debuts Marine Collagen, n.d). The investment supports continuous, high-throughput steps to recover collagen from tuna skin side streams, reported to increase skin hydration, elasticity, and density along with positive results on transepidermal water loss. A recent study on jellyfish collagen peptides found that spray drying, typically following activated-carbon pretreatment, produced uniform spherical particles (≈2–3 μm) with 5% moisture and improved peptides shelf life, compared with irregular freeze-dried flakes at ~8% moisture (Cruz-Padilla et al., 2025). Crucially, spray-drying used ~537 kJ/kg, about 130 times less energy than freeze-drying (~70,000 kJ/kg), while preserving peptide structure and stability, an eco-efficient way to make collagen powders or microcapsules. Acid-soluble collagen solution was atomized into a heated chamber to produce finer, and more consistent dry powder in a continuous process, therefore spray drying is proposed as a scalable alternative to lyophilization. Similarly, Seagarden doubled its spray-drying capacity by installing an additional GEA FSD® dryer and associated process controls, moving drying in-house to shorten the process chain, improve thermal efficiency, capture waste heat and cut transport and handling losses to reduce per-unit energy consumption and operating cost through continuous drying("Seagarden's new spray drying plant for hydrolyzed fish protein," n.d.).

Alternative strategies, such as producing concentrated liquid collagen formulations or stabilized suspensions, can eliminate energy-intensive drying steps altogether and preserve functionality for applications where a liquid feedstock is acceptable.

Critically, the extraction strategy must be tailored to the feedstock. Fresh fish skin and salted, semi-dried codfish skin is biologically and chemically distinct substrates, differing in salt content, proteolytic activity, water content, and overall protein integrity. These differences should guide whether the process targets native triple-helical collagen, gelatin, or hydrolysates as the desired product. Collectively, these considerations underscore the importance of innovative approaches to reduced extraction times, solvent optimization, and careful selection of recovery methods with feedstock-specific strategies. Rethinking the final product form can further eliminate costly and energy-intensive operations while maintaining biomolecular integrity.

3.3. Collagen extraction: Current advances in the use of solvents and technologies

To overcome the limitations of conventional methods, researchers are actively applying other physical and chemical strategies. Ultrasound-assisted extraction (UAE) has demonstrated significant improvements in yield. Low-frequency sonication (20–24 kHz) generates cavitation bubbles that disrupt the fish skin matrix, increasing solvent penetration and enhancing collagen release. In one study, ultrasound nearly tripled collagen yield from yellowfin tuna skin, achieving a 2.7-fold increase compared with acid extraction alone, without compromising the native triple-helical structure when applied for short durations (Pezeshk et al., 2022). Petcharat et al. similarly reported that UAE nearly doubled collagen recovery from Chitala skin, increasing yield from 27% to 57% with no evidence of denaturation (Petcharat et al., 2021).

Microwave-assisted extraction (MAE) is another promising approach, particularly for cold-water fish by-products such as European plaice, where both MAE and ultrasound have been shown to improve hydrolysate yields significantly (Kendler et al., 2023). Pal et al. note that ultrasonic, microwave, supercritical-fluid, and high-pressure extraction are all emerging green technologies for marine collagen recovery, though careful process control is required, as excessive heat can denature sensitive collagen proteins (Pal and Suresh, 2016).

Innovative approaches are under investigation including high-voltage electric discharge (HVED) (Sarkis et al., 2015), pressurized liquid extraction (PLE) (De La Fuente et al., 2021; de la Fuente et al., 2021), microwave assisted extraction (MAE) (Cheng et al., n.d; Kendler et al., 2023; Nguyen et al., 2017), pulsed electric fields (PEF) (Mingyuan

Liu, 2012; Sarkis et al., 2015; Zhang et al., 2020), and supercritical fluid extraction (SFE) (Delikanlı Kıyak et al., 2024), all of which aim to intensify mass transfer and reduce solvent and energy consumption. Despite progresses, a notable scarcity of systematic studies remains, specifically evaluating the effects of these technologies on collagen extraction from fish skin—a critical research gap that demands further exploration.

Other novel techniques are also being explored. Supercritical CO_2 (with a small amount of acidified water) extracted ~13.8% collagen from cod skin under 50 bar pressure (Gaikwad and Kim, 2024). Citric-acid:xylitol:water DES was reported to increase by 2.5 times the yield, Collagen extracted from Blue-shark skin when compared with a conventional acid treatment while reducing extraction time from 96 h to just 1 h (Batista et al., 2022; Gaikwad and Kim, 2024). Such solvents form strong hydrogen-bond networks that selectively solubilize collagen under mild conditions (Bai et al., 2017; Batista et al., 2022; Bisht et al., 2021). Hamdi et al. reported the use of sustainable deep eutectic solvents combined with ultrasonication, achieving a simple, green, and cost-effective method to extract type I collagen from seabass fish scales (Hamdi et al., 2025). An optimized protocol was used by a one-factor-at-a-time approach to maximize yield while preserving secondary structure and the characteristic triple-helical conformation. In addition, in vitro hemolysis and cytotoxicity assays confirmed the biocompatibility of the extracted collagen. Extraction of collagen from beluga sturgeon (*Huso huso*) skin using DES combined with ultrasonication yielded a maximum extraction rate of 24% (Taghitabar et al., 2025). Spectroscopic and structural analyses confirmed the preservation of the triple-helical conformation after DES–ultrasound treatment. Increasing sonication time improved collagen purity, total amino-acid content, thermal stability, water-holding capacity and gel-forming ability, with optimal functional properties observed at a 15-min ultrasound exposure. These results indicate that DES–assisted ultrasonication is an effective approach to enhance both yield and functionality of collagen recovered from beluga skin. A COSMO-RS computational approach was reported by Muhammad et al. to identify the ionic liquid (IL) to be used on collagen dissolution and extraction from fish scale (Muhammad et al., 2017). The COSMO-RS screening identified 1-ethyl-3-methylimidazolium acetate as the optimal IL and it was applied to ground scales pretreated at 100 °C, 12 h. The data confirmed characteristic collagen signatures, fiber dissolution, yet a reduced thermal stability of collagen relative to native scales. Chen et al. reported a green collagen-recovery method for tuna processing waste using a biocompatible IL–based aqueous two-phase system (ATPS) (Chen et al., 2025). They systematically evaluated phase behavior for cholinium-based ionic liquids and the non-ionic surfactant Triton X-100 via phase diagrams, Density Functional Theory calculations, and Nuclear Magnetic Resonance, and optimized single-factor experiments to define the optimal ATPS composition. This method delivered an average collagen yield of approx. 16%, without tedious pretreatment. Spectroscopic characterization confirmed a largely intact triple-helical structure, demonstrating an efficient, safe and sustainable extraction route for tuna processing residues.

Overall, green solvents seemed to boost yield and purity while shortening process times, making them attractive complements to, or replacements for, conventional acid or salt protocols (Batista et al., 2025, 2022; Pezeshk et al., 2022). In practice, these steps can be combined in continuous or semi-continuous systems. Enzymes (pepsin or papain) can be immobilized on a membrane or packed bed to pretreat the raw material in flow, then regenerated and reused, avoiding the need to remove enzyme from the product (Liu et al., 2019). Extrusion–hydroextraction (EHE) as a novel method applied for collagen extraction from tilapia scales yielded approximately three times more yield than the controls (Huang et al., 2016). All extracts were identified as type I collagen by FTIR, SDS–PAGE and molecular-weight distribution analyses, and the material showed potential for food, medical and cosmetic applications (Huang et al., 2016). These techniques markedly increase yield (3 × more collagen than conventional acid extraction) with higher hydroxyproline content and thermal stability) than acid alone.

Other innovative integrated *downstream processes* have been reported such as biomass pretreatment using dehydrated – stabilized fish waste (Themis system, EcoeFISHent project) and solvent recycling (Dondero et al., 2025). Another work reported enzymatic collagen extraction under pressure and recovery by isoelectric method and ultrafiltration which increased the collagen yield up to 11.4% against 5.2% by conventional dialysis (Saallah et al., 2021). Electrodialysis also has been reported as an efficient alternative to conventional dialysis for recovering collagen from *Takifugu flavidus* skin. Electrodialysis reduced purification time and wastewater generation by roughly 95% while delivering high yields (higher than 67 g per 100 g dry weight). Physicochemical characterization indicated the collagen's properties were preserved, tetrodotoxin screening confirmed extract safety, and thermal analysis showed a transition (denaturation temperature) up to 41.8 °C (Chen et al., 2019). A recently disclosed method for deep-sea fish collagen peptides employs a modified microfiltration membrane for purification. The membrane-based process selectively recovers short collagen peptides with an efficiency approaching 99%, offering a high-throughput, scalable route to obtain peptide fractions suitable for food, cosmetic, and biomedical applications (Membrane filtration purification method of deep sea fish collagen peptide, 2023).

To summarize, milling whole biomass with attached scales (Gaikwad and Kim, 2024), green solvents (Batista et al., 2022; Gaikwad and Kim, 2024; Hamdi et al., 2025; Muhammad et al., 2017), integrated downstream process (Dondero et al., 2025), ultrafiltration and isoelectric collagen recovery (Lin et al., 2019; Saallah et al., 2021), continuous solvent or enzyme recycling (Kendler et al., 2023), electrodialysis and microfiltration(Chen et al., 2019; Membrane filtration purification method of deep sea fish collagen peptide, 2023), controlled ultrasonic or microwave assistance during extraction (Pezeshk et al., 2022), and optimized spray drying (Cruz-Padilla et al., 2025; "Seagarden's new spray drying plant for hydrolyzed fish protein," n.d.; Thai Union Debuts Marine Collagen, n.d), are key improvement strategies. Practical and innovative approaches now emphasize minimal solvent use, energy efficiency, and full-chain sustainability to valorize these waste streams within a circular economy approach (e.g., the EU-funded EcoeFISHent project in Liguria, Italy (Dondero et al., 2025)). Collectively, these strategies eliminate the need for energy-intensive cooling, excessive water consumption, and labor-intensive steps, transforming conventional batch-mode lab protocols into a greener, more sustainable pathway for industrialization and commercial collagen production from marine biomass (Table 2).

The proposed framework follows a decision-oriented sequence linking feedstock characteristics, product targets, process design, and industrial feasibility. The starting point is systematic feedstock characterization, where collagen content, lipid and mineral fractions, moisture, and biomass condition are quantified to establish realistic processing windows and predict yield variability. This is followed by early definition of the target product (native collagen, gelatin, or collagen hydrolysates) since structural preservation requirements, purity thresholds, and molecular weight distributions fundamentally dictate extraction severity, downstream purification depth, and overall process economics. Structural integrity monitoring is incorporated throughout processing to verify preservation of the collagen triple helix when native collagen is targeted, or controlled denaturation when gelatin or peptides are desired, ensuring alignment between processing conditions and product specifications. Downstream separation and purification are positioned as a major determinant of industrial feasibility, emphasizing membrane-based fractionation, reduced salt precipitation reliance, and process integration to improve mass balance closure and reduce effluent generation. Scale definition and economic boundary conditions are also introduced to distinguish laboratory optimization from pilot and industrial deployment, allowing evaluation of solvent consumption, throughput constraints, and equipment compatibility

Table 2
A comparative table for conventional and innovative downstream processes.

Traditional method and drawbacks	Innovative (green) approach and benefits	Ref.
Conventional acid extractions (0.5–1.0 M), and slow collagen solubilization. Low yields typically < 5%. NaCl precipitation. Slow, and energy intensive.	Enzyme-assisted (pepsin, papain, or alcalase). Higher yield (64% with pepsin on catfish skin, or 45% with lactic acid). Isoelectric and ultrafiltration recovery. Much shorter time.	(Bisht et al., 2021; S. Chen et al., 2016; Dondero et al., 2025)
Standard solvent extraction by organic acids/alkali which generates neutralization waste, often denatures collagen (producing gelatin). Strong acid produces gelatin (random coils) with limited bioactivity.	DES (cholinium chloride-urea mixtures), efficient and ecofriendly, giving high extraction efficiency. Subcritical water (hot, pressurized water) breaks down proteins rapidly (peptide-rich output). Controlled hydrolysis (enzymes or mild acid) yields defined collagen peptides (1–10 kDa) with high bioactivity and solubility, suitable for nutraceuticals. Combined acid + enzyme or microwave + enzyme can fine-tune peptide size distribution.	(Dondero et al., 2025; Gómez-Guillén and Montero, 2001; Gutierrez-Canul et al., 2025)
Conventional hydrolysis (long-time enzymatic/chemical), slow diffusion limits yield, and high enzyme cost.	Ultrasound or High-Pressure accelerate diffusion and break cell walls. Ultrasound (20–300 W) gave 2.7 × collagen yield vs acid. Pulsed Electric Field (PEF) pretreatment likewise boosts yield.	(Heidari and Rezaei, 2022; Petcharat et al., 2021; Yu et al., 2024; Zhang et al., 2020)
Manual sorting of biomass. Waste must be sorted (skin vs bone vs trimmings), which is laborious.	Integrated processing (Themis dehydration), whole unsorted side streams (skin + fins + heads) can be stabilized and extracted. Dehydrated mixed tuna waste to simplify logistics and omit sorting.	(Bisht et al., 2021; Dondero et al., 2025; Grasso et al., 2023)
Dialysis and precipitation for purification, slow (mainly in days), high water use.	Ultrafiltration membranes concentrate and purify collagen quickly. Ultrafiltration yields ~11.4% from sea cucumber vs 5.2% by dialysis, with similar collagen quality; scalable and less water intensive.	(Shen et al., 2009)
Freeze-drying of collagen, energy-intensive (large CO_2 footprint).	Spray-drying – continuous drying (Seagarden's in-house GEA spray dryer), reducing processing time and transport. Also, fluidized bed drying can replace freeze-dry for pellets and films.	(Dondero et al., 2025)

under realistic operating volumes. The extraction for commercial scale could integrate these constraints and process intensification, considering maturity, scalability, and sustainability.

Preservation of collagen molecular integrity may represent a critical consideration depending on the application, when evaluating such novel extraction technologies and their scalability. Conventional ASC and PSC methods typically maintain the native triple-helical conformation when conducted at low temperatures and mild pH conditions (Bisht et al., 2021; Coppola et al., 2020). In contrast, process-intensified approaches may introduce additional structural risks depending on operating severity (Batista et al., 2022). Based on the fish skin-drived collagen application, it is important to distinguish native collagen from collagen hydrolysates when evaluating extraction outcomes and functional properties. Its native form with retained triple-helical structure and well-preserved molecular order, have different mechanical and gelling properties(Tronci et al., n.d), in contrast, collagen hydrolizates produced through partial or complete cleavage of peptide chains under certain circumstances namely the presence of absence of enzymes or thermal treatments, with or without acidic medium, may result in lower molecular weight fragments with increased solubility and distinct bioactive functionalities (Blanco et al., 2017). For instance, microwave-assisted extraction can generate localized thermal gradients that may promote partial denaturation or hydrolytic cleavage if power density and exposure time are not carefully controlled, while high-intensity ultrasound may induce cavitation-related shear effects capable of altering the molecular organization under prolonged treatment (Cheng et al., n.d; Petcharat et al., 2021). In supercritical fluid extraction, collagen structural preservation is typically maintained under moderate temperature/pressure regimes, and under uncontrolled circumstances can influence conformational stability and product purity (Gaikwad and Kim, 2024). Extraction strategies, process conditions, and intensification methods determine whether native collagen or hydrolysates are recovered, and analytical techniques such as SDS-PAGE, circular dichroism, FTIR spectroscopy, and mass spectrometry help to verify collagen structural integrity, quantify hydrolysis, and ensure accurate assessment of molecular form and functionality of collagen drived from fish skin (Jafari et al., 2020).

Although process-intensification strategies such as ultrasound-, microwave-, and DES-assisted extraction have demonstrated significant laboratory-scale advantages, their industrial translation remains subject to several constraints. Ultrasound-assisted extraction may involve high capital and operational costs associated with power-intensive transducer systems and challenges in achieving homogeneous acoustic cavitation at larger reactor volumes (Petcharat et al., 2021). Microwave-assisted approaches, while reducing extraction time, can introduce risks of collagen denaturation due to localized thermal gradients and present engineering limitations related to penetration depth and reactor scalability (Kendler et al., 2023). Similarly, DES-based extraction systems offer solvent tunability and potential environmental benefits but currently face barriers including limited commercial availability at scale, uncertainties in solvent recovery efficiency, regulatory acceptance, and incomplete techno-economic validation (Bowen et al., 2022). These limitations highlight the need for integrated process design, solvent lifecycle evaluation, and pilot-scale demonstrations to substantiate the industrial feasibility of emerging marine collagen extraction technologies.

Parallel implementation of resource-efficiency metrics including water footprint, solvent recycling efficiency, energy demand, and material loss accounting, enables objective comparison between alternative processing configurations and supports sustainability-driven decision making. Process intensification and circularity considerations are subsequently integrated, promoting continuous extraction concepts, whole-biomass valorization, immobilized enzyme reuse, and solvent recirculation to reduce operational costs and environmental burden. Finally, industrial translation is framed through staged implementation steps encompassing pilot-scale validation, techno-economic assessment, life-cycle considerations, regulatory compliance, and supply-chain integration. Collectively, this framework provides a structured pathway for selecting appropriate collagen product targets and extraction strategies while outlining realistic, data-driven next steps required to transition fish skin collagen processing from laboratory demonstration toward industrial deployment. Due to the limited number of studies reporting detailed cost, energy, and solvent-recycling data for fish skin collagen extraction, a comprehensive quantitative/comparative framework

evaluating implementation costs and solvent recyclability cannot currently be provided. This remains an important area for future investigation.

4. Conclusions

Conventional laboratory-scale marine collagen extraction methods remain constrained by excessive freshwater and salt consumption, labor-intensive pretreatment, and insufficient accounting of collagen losses, collectively limiting industrial feasibility and increasing environmental burden. Further research may highlight the potential of integrated and sustainable approaches, including whole-biomass processing, continuous extraction configurations, solvent recycling, and optimized drying strategies. Successful industrial translation will depend on coordinated process optimization supported by analytical monitoring to preserve molecular integrity and improve mass balance closure. Prioritizing feedstock characterization, clear product targeting, and staged scale-up through pilot validation and techno-economic assessment provides a realistic pathway toward sustainable, large-scale fish skin collagen production for biomedical, nutraceutical, and cosmetic applications.

5. Future perspectives

As previously discussed, while numerous extraction methods are being explored, only a limited number have been successfully applied on an industrial scale. This limitation stems from several factors, including the relatively small range of marine sources investigated so far. The restricted exploration of these sources inevitably hinders researchers' ability to identify and understand alternative collagen sources and types. This lack of knowledge about different types of collagen is undoubtedly slowing progress in developing new biomaterials, devices, and formulations with potential applications in sectors such as cosmetics, pharmaceuticals, and biomedicine, as well as in emerging industries not yet considered.

In addition to exploring new sources, the development of effective extraction processes poses another significant challenge. This involves not only the careful selection of the most appropriate solvents, but also the innovation of precision extraction techniques. The solvent selection should prioritize sustainable options that align with Green Chemistry principles, while maintaining or improving the efficiency of the collagen extraction process. Similarly, precision extraction methodologies must focus on designing downstream processes (including biomass pretreatment, extraction, and purification) capable of selectively isolating collagen from various sources. Importantly, these methods should ensure the preservation of key properties in the final product.

Although this review does not focus on these aspects, we believe that the entire marine collagen value chain could benefit from investigating novel materials, products, and formulations. This includes not only the utilization of native collagen but also its derivatives, such as peptides and collagen blends, to expand the scope of potential applications. Collaborative research across diverse disciplines, such as nanotechnology, chemical engineering, biotechnology, and materials science, supported by artificial intelligence tools, could further drive innovation in the pharmaceutical, cosmetic, and biomedical sectors.

Fig. 4. Future perspectives for exploring technologies related to marine resources, specifically focusing on collagen extraction and other associated by-products.

Within the framework of zero-waste and zero-pollution biorefineries, it is crucial for researchers and industries to prioritize sustainable practices. This includes the use of energy- and time-efficient extraction methods, eco-friendly solvents, closed-loop systems aligned with circular economy principles, and cascade processes that minimize waste and by-products to the greatest extent possible. Adopting biorefinery practices offers significant advantages by enabling the holistic valorization of raw materials, including components beyond collagen.

By incorporating these considerations into the development of extraction processes(as illustrated in Fig. 4) and carefully evaluating raw materials, solvents, methods, and final products, we can contribute to the goals outlined in major environmental and economic policies, such as the European Green Deal (The European Green Deal, n.d.), Circular Economy Action Plan (Circular economy action plan, n.d), Biodiversity strategy for 2030, n.d. (Biodiversity strategy for 2030, n.d.), Farm to Fork Strategy (Farm to Fork Strategy, n.d.), European Bioeconomy Strategy (Bioeconomy Strategy | Knowledge for policy, n.d.), Marine Strategy Framework Directive (EU Marine Strategy Framework Directive, n.d.), and the Zero Pollution Action Plan (Zero pollution action plan, n.d.).

CRediT authorship contribution statement

Abolfazl Keshmirshekan: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Bárbara M.C. Vaz:** Writing – original draft, Formal analysis, Conceptualization. **João A.P. Coutinho:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Sónia P.M. Ventura:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wasman.2026.115758.

Data availability

No data was used for the research described in the article.

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