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MECHANISTIC ROLE OF YELLOWFIN TUNA FISH BONE COLLAGEN PEPTIDES IN WOUND HEALING

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ABSTRACT

Wound healing is a highly complex biological process requiring the coordinated regulation of inflammation, fibroblast activation, angiogenesis, and extracellular matrix (ECM) remodelling. Collagen-derived peptides have received increased attention as bioactive agents capable of accelerating tissue repair; however, the specific peptide sequences and their underlying molecular mechanisms remain insufficiently elucidated. This study aimed to characterize collagen and collagen-derived peptides obtained from yellowfin tuna (Thunnus albacares) bone and to investigate their potential mechanistic roles in wound healing using an integrated proteomic and network pharmacology approach. Pepsin-soluble collagen was successfully extracted from tuna bone with a yield of 4.5%. The extracted collagen showed acceptable physicochemical and microbiological characteristics, including low moisture content (0.97%), absence of detectable Salmonella and Coliform contamination under the tested conditions, and a white, odourless appearance. These results suggest effective drying and basic microbiological acceptability of the collagen preparation. Fourier transform infrared analysis showed characteristic amide A, B, I, II, and III absorption bands that closely corresponded to those of standard collagen, provided supportive spectral evidence. Following tryptic digestion during proteomic sample preparation, liquid chromatography–high resolution mass spectrometry (LC-HRMS) analysis identified 15 collagen-derived peptide sequences enriched in glycine–proline motifs and originating from multiple collagen isoforms. Network pharmacology analysis showed 64 overlapping target genes between the identified peptides and wound-healing–related genes. Protein–protein interaction network analysis highlighted several important hub genes, including MMP9, MMP3, MMP2, MMP13, STAT3, PTGS2, and CXCR4, which have important roles in ECM remodelling, inflammatory regulation, cell migration, and angiogenesis. Gene Ontology and the Kyoto Encyclopedia of Genes and Genomes enrichment analyses indicated significant involvement of major signalling pathways such as IL-17, TNF, NF-κB, and PI3K–Akt, underscoring the multi-target and multi-pathway actions of the peptides. Overall, these results showed that collagen peptides derived from yellowfin tuna bone contribute to wound healing not only as structural ECM components but also as bioactive regulators of important molecular pathways, supporting their potential application as sustainable therapeutic agents and functional biomaterials for wound management.

Key words: Marine peptides, biomaterials, pepsin-soluble collagen, hub genes; nutraceuticals

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INTRODUCTION

Wound healing is a complex physiological process involving haemostasis, inflammation, proliferation, and remodelling. Successful repair requires coordination of fibroblast activation, extracellular matrix (ECM) deposition, angiogenesis, and immune regulation [1]. When disrupted, healing may be delayed, resulting in chronic wounds or pathological scarring [2]. Identifying bioactive compounds that can accelerate repair while modulating inflammation is therefore a major research priority.

Collagen, the most abundant protein in the ECM, has a central role in tissue regeneration [3]. Hydrolysis of collagen yields short-chain peptides that show biological activities beyond structural support. Collagen peptides are known to stimulate fibroblast proliferation, enhance keratinocyte migration, regulate cytokine production, and promote angiogenesis, all important for wound closure [4]. Their glycine- and proline-rich motifs, often containing hydroxyproline, provide both structural stability and recognition by cellular receptors [5]. These properties make collagen peptides attractive candidates for biomedical applications, including functional foods, nutraceuticals, and wound dressings.

Marine sources of collagen are potential alternatives to mammalian collagen because of their better solubility, bioavailability, and lower risk of immunogenicity [6]. Moreover, utilizing fish-processing by-products supports sustainability and reduces waste. Yellowfin tuna (Thunnus albacares), abundant in tropical and subtropical waters, generates large amounts of collagen-rich by-products such as skin and bones. These materials represent an underexploited resource for producing bioactive peptides with potential regenerative functions.

Studies of yellowfin tuna collagen have primarily emphasized its antioxidant and anti-inflammatory properties [7]. Hydrolysates from skin and bone show strong radical-scavenging activity with the DPPH and ABTS assays, along with antimicrobial effects [8]. However, the specific peptides released and their mechanistic contribution to wound healing pathways remain poorly understood. Advanced proteomic tools such as liquid chromatography–high resolution mass spectrometry (LC-HRMS) allow precise identification of peptide sequences, but sequence data alone are insufficient to explain biological activity [9].

Network pharmacology provides a complementary systems-level approach, integrating peptide–target predictions, protein–protein interactions, and pathway enrichment analyses. This method can highlight how bioactive peptides influence processes such as ECM remodelling, angiogenesis using vascular endothelial growth factor A (VEGFA), fibroblast activation through transforming growth factor-

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beta 1 (TGFB1), and inflammation mediated by cytokines including TNF and IL-6 [10].

The present study aimed to characterize peptides derived from yellowfin tuna collagen using LC-HRMS and to investigate their potential role in wound healing using network pharmacology and molecular docking. By linking peptide sequences to molecular targets and pathways, this research seeks to provide mechanistic insights into the regenerative potential of yellowfin tuna collagen peptides (YFTCP) and their applicability as natural agents for wound repair.

METHODS AND MATERIALS

Isolation of Pepsin-Soluble Collagen (PSC)

Pepsin-soluble collagen (PSC) was extracted from yellowfin tuna (Thunnus albacares) bone following the method of Kaewdang *et al*. [11] with slight modifications. Briefly, fresh yellowfin tuna bone by-products were obtained from PT Winson Prima Sejahtera, Deli Serdang Regency, North Sumatra, Indonesia 20251. The bones were collected from yellowfin tuna with an approximate body weight of 40–100 kg and body length of 150–200 cm. The bone samples were manually cleaned to remove adhering muscle and connective tissues, cut into small pieces of ~1–2 cm using a stainless-steel knife, washed thoroughly with cold distilled water, and used as the raw material for collagen extraction. To remove non-collagenous proteins, the samples were soaked in 0.1 M NaOH solution at a sample-to-solution ratio of 1:8 (w/v) for 6 h at 4 °C with continuous stirring. The NaOH solution was replaced at 3 h. The samples were then repeatedly washed with cold distilled water until the rinsing water reached neutral pH, which was verified using a calibrated pH meter. The pretreated samples were further soaked in 0.5 M ethylenediaminetetraacetic acid (EDTA), pH 7.4, at a sample-to-solution ratio of 1:8 (w/v) for 24 h at 4 °C with continuous stirring to remove mineral components. The EDTA solution was replaced at 12 h. After demineralization, the samples were washed three times with cold distilled water before collagen extraction. For PSC extraction, pretreated samples were treated with 0.5 M acetic acid containing 1.5% (w/w) pepsin from porcine gastric mucosa (Sigma-Aldrich (M) Sdn. Bhd., Selangor, Malaysia) at a sample-to-solution ratio of 1:40 (w/v). The extraction was done for 30 h at 4 °C with continuous stirring. The extract was then centrifuged at 9,000 × g for 30 min at 4 °C using a refrigerated centrifuge (TGL-16, Chenlee, Changsha, China). The resulting supernatant was carefully collected for further processing. The residue was re-extracted with 0.5 M acetic acid containing 1.5% (w/w) pepsin for 12 h using the same temperature, stirring, and centrifugation conditions. The two supernatants were combined, and solid NaCl was added until the final concentration reached 0.7 M to precipitate collagen. The mixture was centrifuged at 2,500 × g for 15 min to obtain the precipitate. The precipitated collagen was transferred into a dialysis bag

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with a molecular weight cut-off (MWCO) of 1,200–1,400 Da (MD44-5M, MYM Biological Technology Co., Ltd., Massachusetts, USA) and dialyzed against distilled water at 4 °C to remove residual salts and acetic acid. The dialyzed collagen was frozen at −80 °C overnight and subsequently lyophilized using a freeze dryer (BIOBASE, Jinan, China) to obtain dried pepsin-soluble collagen.

Moisture Content and Physical Appearance

The moisture content of the extracted collagen was determined to evaluate the drying efficiency of the lyophilized collagen sample. The dried collagen sample was weighed and analysed for moisture content using a gravimetric method by drying at 105 °C for 3 h until a constant weight was obtained. The result was expressed as percentage moisture content. In addition, the physical appearance of the collagen was evaluated descriptively based on colour and odour. These observations were used only as preliminary physical quality indicators and were not interpreted as direct evidence of collagen purity [12].

Microbiological Analysis

Microbiological analysis was done to evaluate detectable Salmonella and Coliform contamination in the extracted collagen sample. All procedures were carried out aseptically. Briefly, 1 g of dried collagen sample was aseptically transferred into 9 mL of sterile buffered peptone water (HiMedia, Mumbai, India) and homogenized thoroughly by Vortex (B-One, Jakarta, Indonesia) mixing to obtain an initial 10^{-1} suspension. For Salmonella screening, the sample suspension was pre-enriched in buffered peptone water (HiMedia, Mumbai, India) and incubated at 37 °C for 18–24 h. After incubation, one loopful of the enriched culture was streaked onto Salmonella–Shigella agar (HiMedia, Mumbai, India) and incubated at 37 °C for 24–48 h. The plates were examined visually for suspected Salmonella colonies, which are typically colourless or translucent colonies with or without black centres due to hydrogen sulphide production.

For Coliform screening, an aliquot of the prepared sample suspension was inoculated onto eosin methylene blue agar (HiMedia, Mumbai, India) and incubated at 37 °C for 24–48 h. The plates were examined visually for suspected Coliform colonies, which appear as dark colonies, sometimes with a metallic green sheen in the case of Escherichia coli. The microbiological results were expressed qualitatively as detected or not detected based on the presence or absence of characteristic colonies on the selective media [12].

Fourier Transform Infrared Spectroscopy [FTIR] Analysis

FTIR analysis was done to identify the major functional groups of the extracted collagen and to compare its spectral profile with that of standard collagen. The dried collagen sample and a commercial type I collagen standard derived from tilapia scale

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(Personal Formula Resources Sdn. Bhd., Shah Alam, Selangor, Malaysia) were analyzed by FTIR spectroscopy over the wavenumber range of 4000–500 cm^{-1}. The main absorption bands observed in the spectra were assigned to characteristic collagen amide bands, including amide A, amide B, amide I, amide II, and amide III. The FTIR spectra were used to evaluate the presence of collagen-related functional groups and to provide preliminary structural information on the extracted collagen [13].

Proteomic Sample Preparation

Proteomic sample preparation and LC-HRMS analysis were done according to the proteomics workflow of Corpora Science, Yogyakarta, Indonesia. Briefly, 100 mg of collagen was mixed with 500 µL of 50 mM ammonium bicarbonate buffer at pH 8.0 (Fisher Chemical, Pittsburgh, Pennsylvania, United States). The mixture was mixed for 1 min using a Thermo Scientific Digital Vortex Mixer (Waltham, Massachusetts, United States). Protein reduction was done by adding 10 µL of 100 mM dithiothreitol (DTT; Sigma-Aldrich), followed by incubation for 1 h at 55 °C and 1000 rpm using an Eppendorf Thermomixer C (Hamburg, Germany). Alkylation was done by adding 10 µL of 100 mM iodoacetamide (IAA; Sigma-Aldrich), followed by incubation for 1 h in the dark. Proteolytic digestion was then done by adding 10 µL of MS-grade trypsin (Pierce, Thermo Scientific, Rockford, Illinois, United States), followed by incubation for 17 h at 37 °C using the Thermomixer C. The digestion reaction was stopped by adding 500 µL of 1% trifluoroacetic acid (TFA; Merck, Darmstadt, Germany). The sample was centrifuged at 8,100 × g for 10 min using an Eppendorf Centrifuge 5430 R (Eppendorf AG, Hamburg, Germany), filtered through a 0.2 µm polyvinylidene fluoride (PVDF) syringe filter (Captiva, Agilent Technologies, Santa Clara, California, United States), and transferred into LC-HRMS sample vials before injection [14].

LC-HRMS

Peptide analysis was done using a Thermo Scientific Vanquish Horizon ultra-high-performance liquid chromatography (UHPLC) system equipped with a binary pump (Germering, Germany). Chromatographic separation was carried out using a Thermo Scientific Acclaim PepMap 100 C18 analytical column with a length of 150 mm, internal diameter of 1 mm, and particle size of 3 µm (Vilnius, Lithuania). The mobile phases consisted of solvent A, mass spectrometry-grade water containing 0.1% formic acid, and solvent B, mass spectrometry-grade acetonitrile containing 0.1% formic acid; both solvents were obtained from Fisher Chemical (Pittsburgh, Pennsylvania, United States).

The flow rate was maintained at 75 µL/min, the total run time was 45 min, the column temperature was set at 30 °C, and the injection volume was 5 µL. The gradient program was set as follows: 5% solvent B for 1 min, 5–50% solvent B for 30 min,

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held at 50% solvent B for 2 min, increased to 90% solvent B for 2 min, and returned to 5% solvent B until the end of the 45-min run. High-resolution mass spectrometry was done using a Thermo Scientific Orbitrap Exploris 240 high-resolution mass spectrometer (HRMS; Bremen, Germany) in positive ion mode. Data were acquired using full mass spectrometry/data-dependent tandem mass spectrometry acquisition mode (Full MS/dd-MS²). Full MS acquisition was done at a resolution of 120,000 full width at half maximum (FWHM), with a scan range of 350–1,500 m/z, maximum injection time of 100 ms, intensity threshold of 8000, charge states of 2–6, and mass tolerance of 5 ppm. For dd-MS² acquisition, the resolution was set at 15,000 FWHM and the normalized collision energy was 30. Nitrogen was used as the collision gas.

Ionization was done using an OptaMax NG Heated Electrospray Ionization (H-ESI) (Thermo Fisher Scientific, Bremen, Germany). The spray voltage was set at 4000 V in positive mode. The sheath gas, auxiliary gas, and sweep gas were set at 10, 5, and 1 arbitrary units (AU), respectively. The ion transfer tube temperature was maintained at 300 °C. Data analysis was done using Thermo Scientific Proteome Discoverer 2.5 software (San Jose, CA, USA) with the Sequest HT search engine. Peptide identification was done by searching against the UniProt and NCBI databases [14,15].

Network Pharmacology

Peptides identified from the LC-HRMS were analysed for potential protein targets using the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/), with emphasis on biological processes related to cancer, oxidative stress, and inflammation. The predicted targets were subsequently imported into the STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins; STRING Consortium, https://string-db.org/) to construct protein–protein interaction (PPI) networks. The analysis was done using Homo sapiens as the reference organism, with the minimum required interaction score set at medium confidence (0.400). Hub proteins were then identified based on topological parameters, including degree, betweenness centrality, and closeness centrality. To further elucidate the biological significance of the identified targets, Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the STRING database (version 12.0). Statistical significance was set at an FDR-adjusted p value < 0.05. Network visualization and modular analysis were done using Cytoscape 3.8, (Cytoscape Consortium, San Diego, CA, USA), where clusters were detected using the MCODE algorithm and correlated with enriched GO terms and KEGG pathways to provide a systems-level overview of the functional mechanisms associated with the peptides [16].

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RESULTS AND DISCUSSION

Yield of Collagen

The extraction of pepsin-soluble collagen (PSC) from yellowfin tuna (Thunnus albacares) bone produced a collagen yield of 4.5% based on the initial wet weight of the bone sample, as shown in Table 1. This result indicates that yellowfin tuna bones can serve as a potential raw material for collagen recovery, particularly when processed using pepsin-assisted extraction.

The collagen yield obtained was within the range reported for several marine collagen sources, including tilapia, catfish, and cod collagen, although direct comparison should be interpreted carefully because collagen recovery is influenced by species, tissue type, mineral content, pretreatment procedures, enzyme concentration, solvent ratios, extraction temperatures, and extraction duration [17,18]. In bone-derived materials, demineralization and removal of non-collagenous proteins are particularly important because the inorganic matrix may reduce collagen extractability.

From a sustainability perspective, yellowfin tuna bone is an important fish-processing by-product. In the tuna processing and canning industries, edible muscle is the main product, while bones, heads, viscera, skin, and other residues are commonly by-products. Therefore, the recovery of collagen from tuna bone may provide added value to fish-processing waste and support the development of marine-derived collagen peptides for further functional or biomedical investigation. One such potential application is wound management. However, further optimization and quality characterization are required before its application in wound-management products.

Characterization of Yellowfin Tuna Collagen

The extracted collagen from yellowfin tuna bone was evaluated for moisture content, microbiology, and physical appearance. As shown in Table 2, the extracted collagen had a low moisture content of 0.97%, indicating effective dehydration after freeze-drying. Low moisture content may contribute to improved storage stability by reducing water availability; however, this parameter does not directly indicate collagen purity or structural integrity [12]. Microbiological testing showed no detectable Salmonella or Coliform contamination under the tested conditions, as shown in Figure 1. These results indicate that the extracted collagen met the microbiological parameters studied. However, the absence of detectable Salmonella and Coliforms does not mean that other harmful microbes were not present. The extracted collagen appeared white and odourless, indicating an acceptable physical appearance of the dried collagen preparation.

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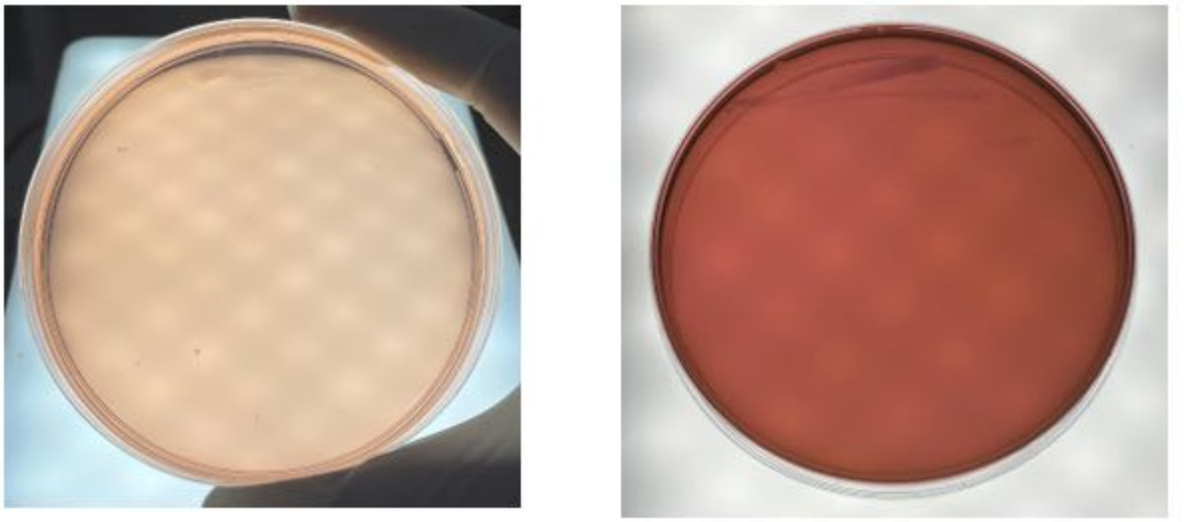

SSA (Salmonella Shigella Agar) Eosin Methylene Blue Agar (EMBA)

Figure 1: Qualitative microbiological screening of extracted yellowfin tuna bone collagen for Salmonella and Coliforms contamination using selective agar media

FTIR Analysis

The FTIR spectra of the bone collagen and the commercial type I collagen standard are shown in Figure 2. The extracted collagen showed absorption bands corresponding to the main collagen-related amide regions, including amide A, amide B, amide I, amide II, and amide III. The overall similarity between the extracted collagen spectrum and the commercial collagen standard indicates that the extracted collagen had comparable major functional group characteristics.

A broad absorption band observed around 3300–3400 cm^{-1} was assigned to the amide A region, which is commonly associated with N–H stretching vibrations and hydrogen bonding. The absorption band near 2930 cm^{-1} corresponded to the amide B region, which is attributed to asymmetric stretching of CH_2 groups. The amide I band was observed at 1640.35 cm^{-1} in the reference collagen spectrum and at 1643.85 cm^{-1} in the extracted collagen spectrum. This band primarily represents C=O stretching vibrations of peptide bonds and is sensitive to the hydrogen-bonding environment of the collagen backbone. The close peak positions between the two spectra suggest that the extracted collagen retained a protein secondary structure comparable to that of the reference collagen. However, precise assignment of individual secondary-structure components would require band deconvolution or second-derivative analysis. The amide II band around 1500–1600 cm^{-1} corresponds mainly to N–H bending and C–N stretching vibrations, while the amide III band from 1200–1300 cm^{-1} is related to C–N stretching and N–H deformation.

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The presence of these characteristic amide bands supports the identification of collagen-related functional groups in the extracted yellowfin tuna bone collagen. However, because no additional structural confirmation analysis was done, the FTIR results should be interpreted as supportive spectral evidence rather than definitive proof of complete triple-helix preservation [19]. Therefore, the FTIR results indicate that the extracted collagen showed characteristic collagen-associated absorption bands and a spectral profile comparable to the commercial type I collagen standard.

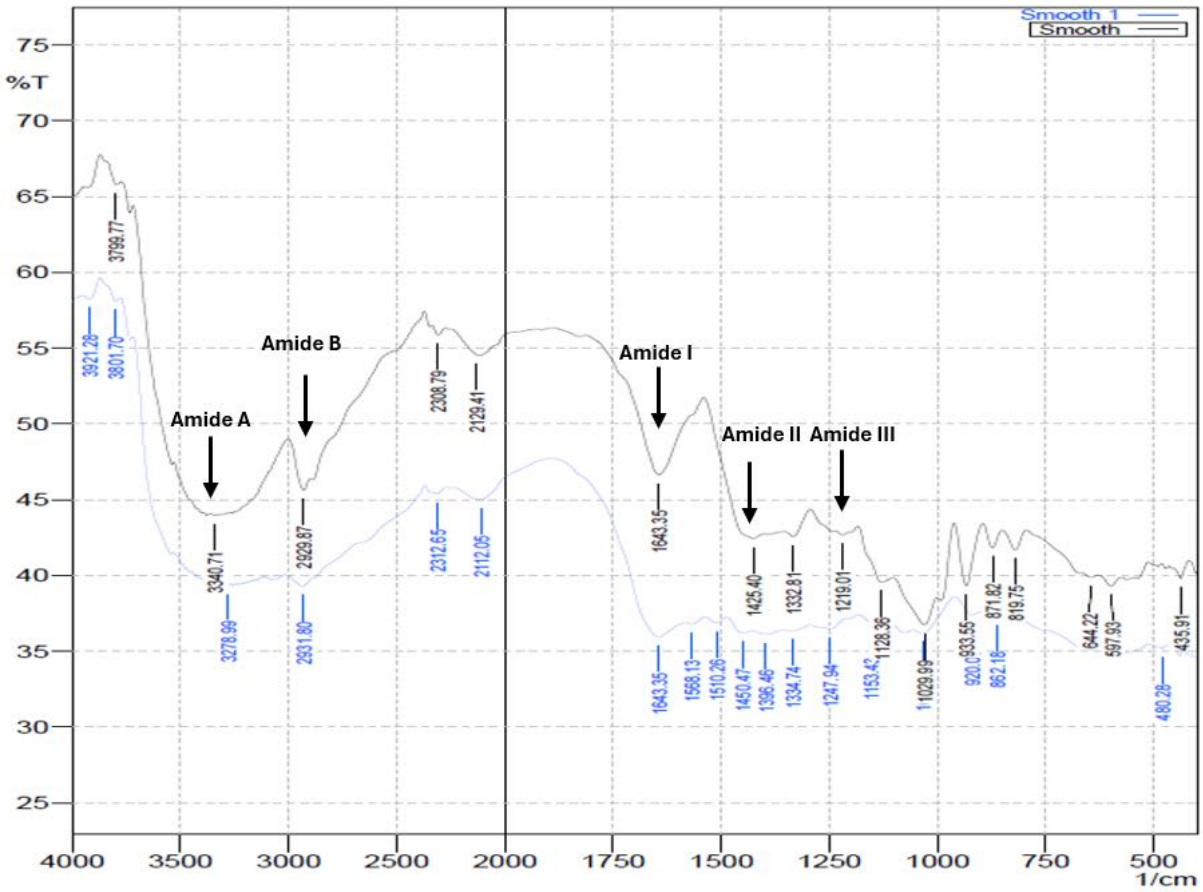

Figure 2: FTIR spectra of extracted yellowfin tuna bone collagen (blue line) and commercial collagen standard (gray line)

Determination of Collagen Peptides

The pepsin-soluble collagen was used for proteomic sample preparation and analysed using LC-HRMS. The total ion chromatogram (TIC) profile is shown in Figure 3. The TIC represents the overall ion intensity detected by the mass spectrometer across the chromatographic run. Peaks appearing at different retention times indicate peptide-related ion signals separated during liquid chromatography before mass spectrometric detection. A total of 15 distinct peptide sequences were successfully identified, originating from multiple collagen α-chain isoforms, including types I, IV, V, IX, XI, XII, XIII, XIV, XV, XVIII, and XXVII. These peptides were

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enriched in glycine–proline–hydroxyproline motifs, characteristic of collagen-derived peptides, which are strongly associated with fibroblast proliferation, keratinocyte migration, extracellular matrix stabilization, and angiogenesis [20]. The detailed peptide sequences and their corresponding protein chains are shown in Table 3.

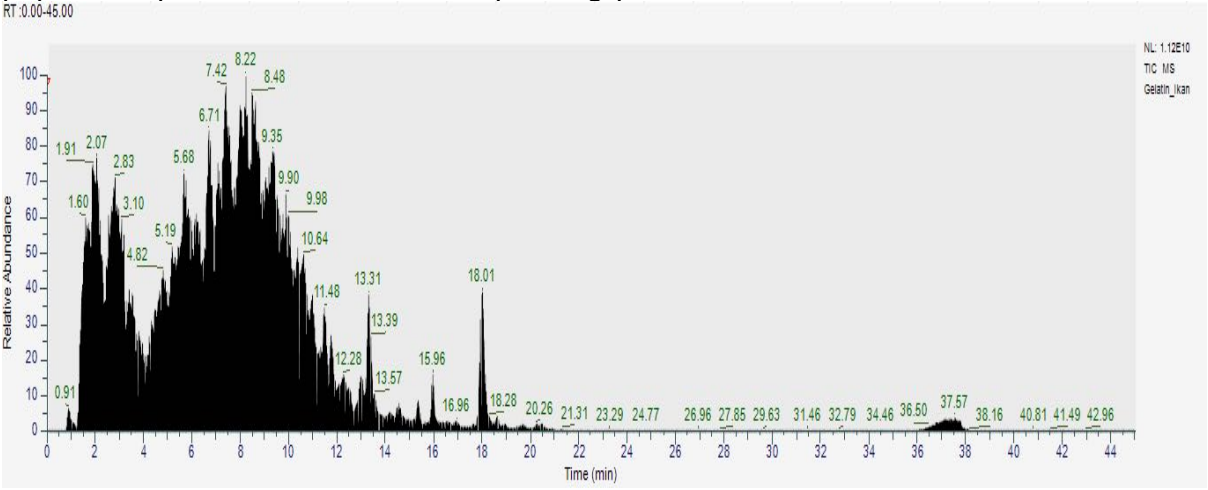

Figure 3: Total ion chromatogram (TIC) of collagen-derived peptides from yellowfin tuna (Thunnus albacares) bone analysed using LC-HRMS

The identification of 15 distinct peptide sequences from yellowfin tuna collagen highlights the structural diversity of marine-derived bioactive peptides. Each collagen type contributes differently to wound-healing processes. Type I collagen peptides (α1a, α1b) are abundant in bone and skin, having a central role in ECM remodelling and tensile strength [21]. Type IV collagen peptides (α5 and α6 chains) are important components of basement membranes, supporting cell adhesion, keratinocyte migration, and angiogenesis [22]. Type V collagen peptides regulate fibril diameter and are important for fibroblast activity and scar tissue organization [23].

Type XII, XIII, XIV, and XV peptides are associated with fibril interaction, endothelial cell function, and vascular remodelling, indicating their role in promoting angiogenesis and tissue vascularization [24]. Type XVIII collagen peptides have been linked to anti-angiogenic fragments (endostatin), but their peptide fragments can also modulate vascular growth in a wound microenvironment [25]. Type XXVII collagen is expressed during development and tissue regeneration, suggesting a role in matrix organization during repair phases [26]. Together, these peptide profiles show that tuna bone collagen not only provides structural amino acids but also generates bioactive fragments that have been previously shown [24] to regulate multiple pathways, including fibroblast proliferation, keratinocyte migration, angiogenesis, and immune modulation, all important for accelerated wound healing.

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Genes of Collagen Peptides that Target Wound Healing

The Venn diagram analysis (Figure 4) showed 64 overlapping target genes between the predicted bioactive targets of yellowfin tuna collagen peptides and wound healing-associated genes. Including non-overlapping target genes, 36 were unique to collagen, while 6,177 were specific to wound healing. The intersection highlights a potentially biologically relevant overlap, suggesting that collagen-derived peptides may act on important molecular regulators involved in tissue repair and regeneration.

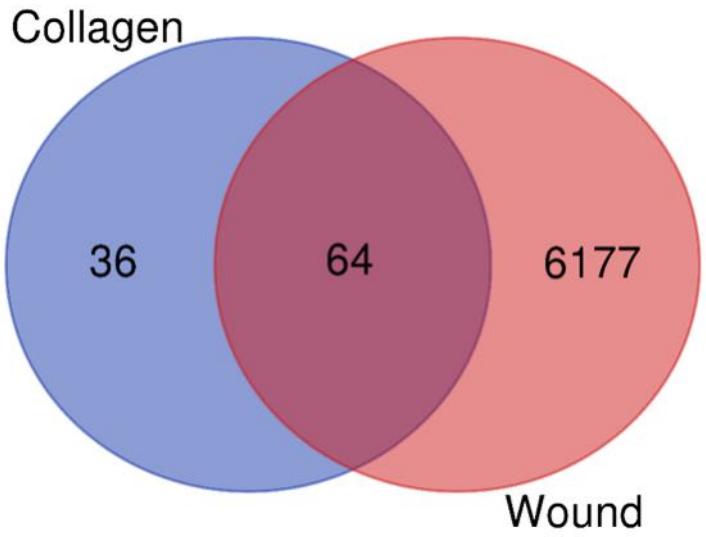

Figure 4: Venn diagram of predicted collagen-peptide targets and wound-healing-associated genes. The diagram shows 36 collagen-specific genes, 6,177 wound-healing-specific genes, and 64 overlapping genes used for subsequent PPI and enrichment analyses

The shared targets included VEGFA, TGFB1, TNF, IL6, MMP9, and EGFR, which are central to angiogenesis, fibroblast activation, inflammatory modulation, and extracellular matrix remodelling [27] These genes are important drivers of wound healing, being involved in fibroblast proliferation, keratinocyte migration, vascularization, and balanced tissue remodelling. Thus, the 64 overlapping genes indicate that collagen peptides from yellowfin tuna bone have the potential to influence wound-healing mechanisms not only structurally, but also through molecular pathways that accelerate tissue repair.

PPI Analysis using STRING DB and Cytoscape

The 64 overlapping target genes were further analysed using the STRING database to construct a PPI network (Figure 5). The visualization showed a dense interconnectivity among the nodes, suggesting that most of the genes are functionally correlated and may cooperate to regulate biological processes important for tissue repair. This systems-level approach highlights the synergistic role of

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collagen peptides in modulating multiple molecular pathways simultaneously, rather than acting through a single target.

Topological analysis identified several hub genes with high degree values, where degree refers to the number of connections or interactions of a gene within the PPI network. These hub genes included MMP9, MMP3, MMP2, MMP13, STAT3, PTGS2, CXCR4, CTSB, MMP1, and MMP7 (Figure 5, Table 4) and are closely associated with extracellular matrix remodelling, inflammation, angiogenesis, and fibroblast activation. Among them, MMP9 was the most interconnected node, indicating its potentially pivotal role in balancing tissue degradation and regeneration during wound healing. The identification of these hub genes provides mechanistic insights into how yellowfin tuna collagen peptides may accelerate wound closure and improve tissue repair outcomes.

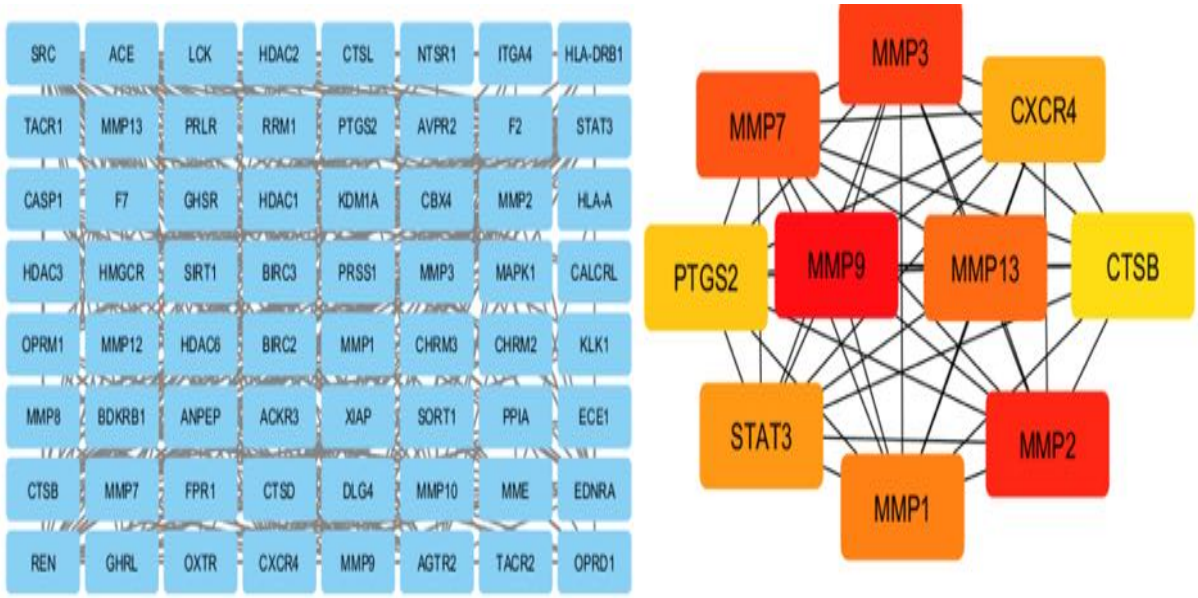

Figure 5: Protein–protein interaction (PPI) network of the 64 overlapping genes between collagen-derived peptide targets and wound-healing-associated genes. The network was constructed using the STRING database and visualized using Cytoscape. The highlighted hub genes represent the top ten genes with the highest number of protein interactions in the network

The hub genes identified in Table 4 suggest the multifaceted mechanisms through which collagen peptides contribute to wound healing. The dominance of matrix metalloproteinases (MMP) such as MMP9, MMP3, MMP7, MMP13, MMP2, and MMP1 highlights the central role of collagen peptides in extracellular matrix (ECM) remodelling [28]. These enzymes regulate the controlled degradation of fibrillar and basement membrane collagens, a prerequisite for fibroblast migration, angiogenesis, and new tissue formation [29]. Among the identified targets, matrix

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metalloproteinase-9 (MMP-9) was the most interconnected hub and is involved in immune-cell infiltration and extracellular-matrix turnover. This finding is consistent with earlier reports showing that marine collagen peptides accelerate wound closure by enhancing fibroblast and keratinocyte activity [30].

In addition to ECM modulation, other hub genes indicate possible complementary mechanisms related to wound healing. The PTGS2 gene, which encodes cyclooxygenase-2 (COX-2), may contribute to prostaglandin-mediated inflammatory regulation and re-epithelialization. COX-2-derived eicosanoids and prostaglandin E2 (PGE2) signalling have been linked to keratinocyte proliferation and migration during wound repair [31]. Signal transducer and activator of transcription 3 (STAT3) may also contribute to wound-healing-related cellular responses. Previous studies have shown that STAT3 signalling is involved in skin wound healing, particularly keratinocyte migration, inflammatory signalling at the wound edge, and re-epithelialization [32].

These results suggest that PTGS2 and STAT3 may be related to regulatory events occurring during the transition from the inflammatory phase to the proliferative phase, which is an important step in normal wound healing [33]. Meanwhile, CXCR4 may contribute to wound repair through CXCL12/CXCR4-mediated recruitment of stem or progenitor cells and through its involvement in cell migration and angiogenesis-related tissue repair processes [34]. In the hub-gene analysis, cathepsin B, encoded by the CTSB gene, may reflect a protease-related remodelling mechanism. Cathepsin B has been reported to contribute to extracellular-matrix remodelling and keratinocyte migration during wound healing; therefore, its identification as a hub gene may indicate involvement in proteolysis-associated tissue remodelling [35].

GO and Pathway Enrichment Analysis

The enrichment analysis of the 64 overlapping genes provided insights into their biological relevance in wound healing (Figure 6). The KEGG pathway analysis (Figure 6A) showed that the most significantly enriched pathways were the IL-17, TNF, NF-κB, calcium, and PI3K–Akt signaling pathways. These signaling cascades are known regulators of inflammation, angiogenesis, and extracellular matrix (ECM) remodeling [36]. Among them, the IL-17 signaling pathway was one of the most prominent, highlighting its importance in controlling immune responses and cytokine production during tissue repair.

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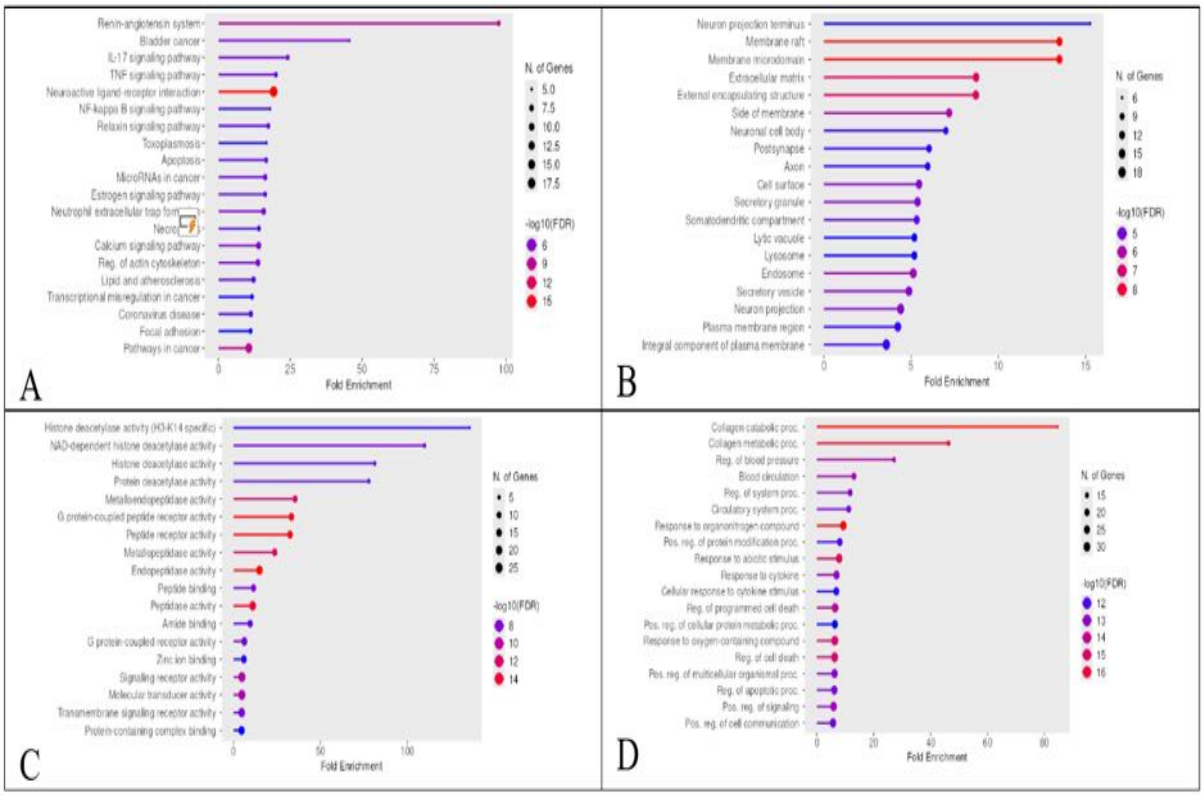

Figure 6: KEGG pathway and gene ontology (GO) enrichment analysis of the 64 overlapping genes. (A) KEGG pathway enrichment; (B) GO cellular component (GO-CC); (C) GO molecular function (GO-MF); and (D) GO biological processes (GO-BP)

Gene Ontology (GO) classification supported these results across three levels. At the cellular component (CC) level (Figure 6B), enrichment was observed in extracellular matrix, membrane raft, and secretory granule, reflecting the structural and signaling roles of collagen peptides in tissue repair. At the molecular function (MF) level (Figure 6C), the hub genes were strongly associated with metalloendopeptidase activity, protein binding, and receptor activity, suggesting active involvement in proteolysis and receptor-mediated signal transduction. At the biological process (BP) level (Figure 6D), enrichment included the collagen catabolic process, regulation of angiogenesis, blood circulation, and response to oxidative stress. These biological processes are consistent with the dynamic requirements of wound healing from matrix degradation to tissue regeneration.

Further exploration of the IL-17 signaling pathway (Figure 7) showed that several wound healing-related mediators were involved, including IL6, TNF, CXCL8, and MMP9. These genes are central in regulating inflammation, immune cell recruitment, and ECM remodelling [37]. Their coordinated activation by collagen peptides suggests a role in accelerating the resolution of inflammation, thereby allowing timely

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progression to the proliferative phase of wound healing. Dysregulation of this pathway is often linked with chronic wounds or excessive scarring, which underscores the therapeutic potential of collagen-derived peptides in maintaining balance within the inflammatory microenvironment.

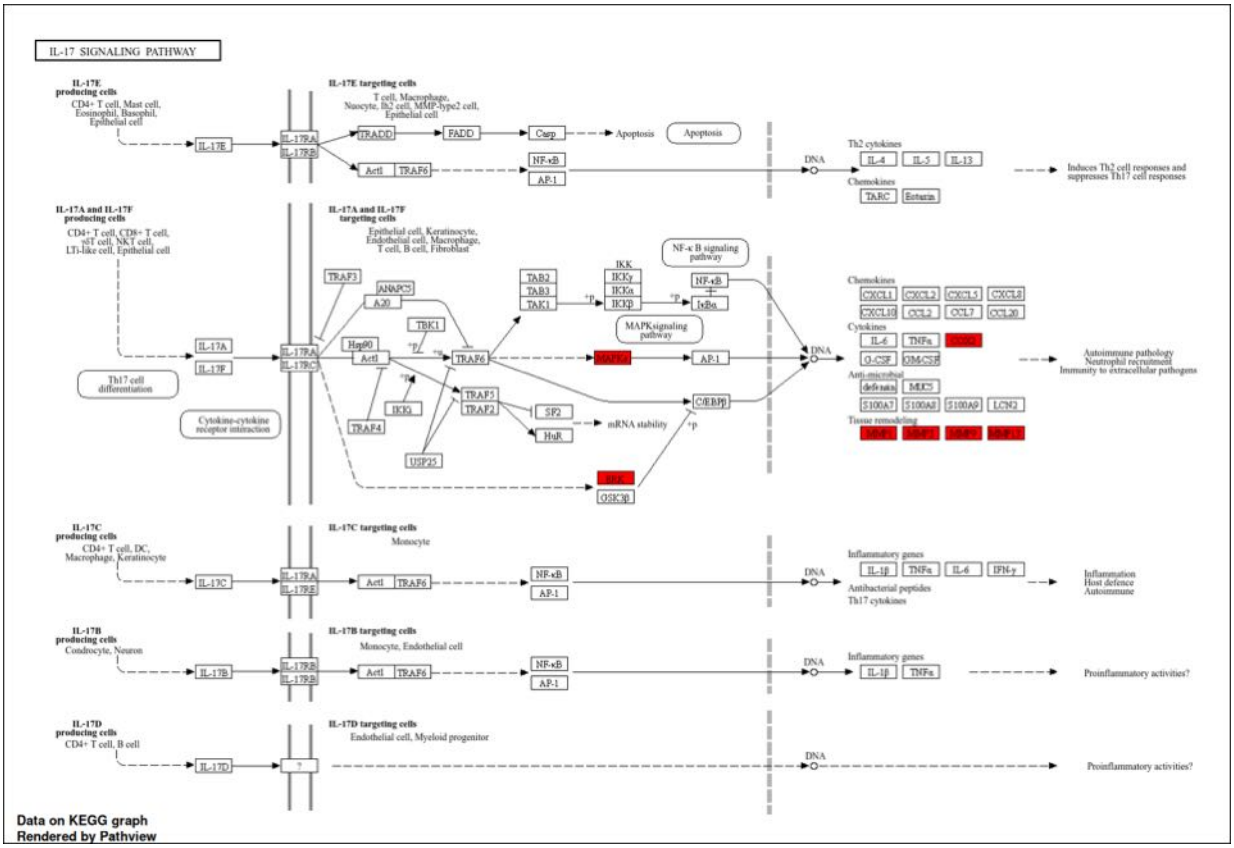

Figure 7: KEGG pathway IL-17 signalling pathway associated with wound healing

Taken together, the GO and KEGG enrichment analyses show that these collagen peptides act through multi-targeted and multi-pathway mechanisms. Rather than functioning solely as structural substrates, these peptides modulate molecular pathways that integrate inflammation, angiogenesis, fibroblast activation, and ECM remodelling [38]. This systems-level evidence reinforces the potential of marine collagen peptides as effective natural agents for wound healing, supporting their application in functional foods, nutraceuticals, and advanced wound care products.

CONCLUSION AND RECOMMENDATIONS FOR DEVELOPMENT

Yellowfin tuna (*Thunnus albacares*) bone yielded 4.5% collagen with acceptable preliminary physicochemical and microbiological characteristics across the tested parameters. LC-HRMS identified 15 collagen-derived peptide sequences from multiple collagen isoforms. Network pharmacology analysis identified 64 overlapping target genes and important hub genes, including MMP9, STAT3, and VEGFA, which

were associated with extracellular matrix remodelling, angiogenesis, and inflammatory regulation. These results suggest that yellowfin tuna bone collagen peptides may have potential relevance to wound-healing-related mechanisms and warrant further experimental validation.

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Competing interests

The authors declare no conflicts of interest.

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Table 1: Yield of collagen extracted from yellowfin tuna bone

Sample	Bone weight (g)	Collagen yield (g)	Yield (%)
Yellowfin tuna bone	500	22.6	4.5

Table 2: Physicochemical and microbiological characterization of yellowfin tuna bone collagen

Parameter	Yellowfin tuna collagen
Moisture content (%)	0.97%
Salmonella contamination	Absent
Coliform contamination	Absent
Colour and odour	White, odourless

Table 3: Tuna fish bone collagen peptides detected from *Thunnus albacares collagen*

No	Sequence	Protein/chain
1	GAPGEKGPMGPAGRDGIQGPVGLPGPAGPQGP PGEDGDK	Alpha-1(XII) chain isoform X1
2	YEVSVYAQYDKADSLPVTGYETTVEER	Alpha-1(XIII) chain isoform X1
3	GKPGEPGPAGPAGPEGPRGEGGVMGFSGPKG DK	Alpha-1(XIV) chain isoform X1
4	GDRGEPGPVGPTGPVGDIGVPGPQGPQGPQGP SGRSIMGPPGAQGER	Alpha-1(XXVII) chain B isoform X1
5	GIAGEPGPAGPPGTIGPLGEMGLMGLPGRDGER	Alpha-2(XI) chain isoform X8
6	GEPAVLEPGMLIEGPPGPEGPAGPTGPPGHSGP PGSVGDPGERGPPGR	Alpha-5(IV) chain isoform X1
7	GLAGSPGQPGFPGQKGDPGSPGFSGPSGIPGG PGAK	Alpha-6(IV) chain isoform X1
8	DGVPGSPGYPGQKGERGYPGLPGAPGPSYPAS YAEK	Type XVIII alpha 1a isoform X1
9	VGPQGGPGLPGQAGFPGPIGPKGDRGEPGTPG YGSK	Type I, alpha 1a isoform X1

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10	GDRGDQGAK; GAPGPSGPSGPQGFTGPPGEPGEPGPAGAMG PRGAAGPPGKNGEDGESGKPGR; GFSGLDGAK	Type I, alpha 1b isoform X1
11	GFTGMQGLPGTPGSMGERGPAGASGPAGPRG PAGSSGSPGK; GAAGESGKPGER; GAPGIGGPTGPR; GFSGLDGAK	Type IX, alpha 1a
12	GQVGPPGPAGAR	Type V, alpha 3a isoform X1
13	EGKQGMKGAK	Type XI, alpha 1a isoform X6
14	DGLPGHPGQRGETGFQGKTGPPGPGGVVGPQ GPTGETGPVGER	Type XV, alpha 1b isoform X1
15	GPSGPPGPPGPPGPPGTKFFVEDMEGSGK	Type XV, alpha 1b isoform X1

Table 4: Top 10 hub genes identified in the PPI network between collagen peptides and wound healing

No	Gene	Protein name	Main function in wound healing
1	MMP9	Matrix metalloproteinase-9	Extracellular matrix (ECM) remodelling, collagen degradation, and facilitation of immune cell and fibroblast migration to the wound site.
2	MMP3	Matrix metalloproteinase-3 (Stromelysin-1)	Degradation of ECM components, activation of pro-MMP, and support of tissue remodelling.
3	MMP7	Matrix metalloproteinase-7 (Matrilysin-1)	Breakdown of elastin and proteoglycans; activation of growth factors released at the wound site.
4	MMP13	Matrix metalloproteinase-13 (Collagenase-3)	Degradation of type I, II, and III collagens; important for late-stage matrix remodelling.
5	MMP2	Matrix metalloproteinase-2 (Gelatinase A)	Degradation of type IV collagen, facilitating fibroblast migration and angiogenesis.
6	MMP1	Matrix metalloproteinase-1 (Collagenase-1)	Breakdown of fibrillar collagen; triggers ECM remodelling for new tissue formation.

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7	PTGS2	Prostaglandin-endoperoxide synthase-2 (COX-2)	Regulation of inflammation; prostaglandin synthesis that modulates vasodilation and immune cell infiltration.
8	STAT3	Signal transducer and activator of transcription-3	Transcription factor regulating cell proliferation, keratinocyte migration, angiogenesis, and immune responses.
9	CXCR4	C-X-C Chemokine receptor type 4	Chemokine receptor mediating progenitor cell recruitment and angiogenesis using the SDF-1/CXCR4 axis.
10	CTSB	Cathepsin B	Lysosomal protease involved in matrix degradation and activation of other enzymes during remodelling.

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