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Biomedical potential and applications of fish collagen: an integrative literature review

Potencial biomédico e aplicações do colágeno de peixe: uma revisão integrativa da literatura

Potencial biomédico y aplicaciones del colágeno de pescado: una revisión bibliográfica integral

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ABSTRACT
In view of the growing demand for sustainable and safe biomaterials, this integrative review study aims to investigate the biomedical applications of fish-derived collagen by analyzing studies published between 2019 and 2024. The PubMed and Web of Science databases were searched using descriptors from DeCS/MeSH (Fish, Collagen, Potential Biomedical, and Applications). The Research Rabbits tool was also used to assist in the selection of relevant journals. After rigorous application of inclusion and exclusion criteria, 9 studies were selected. The studies indicate that fish collagen has promising potential with therapeutic advantages over traditional collagens, such as lower risk of contamination and allergic reactions, including wound healing, tissue regeneration, fabrication of hydrogels and collagen sponges for applications in biomedical devices. However, challenges remain related to the standardization of extraction methods and variability between fish species. It is concluded that, with the improvement of techniques and the overcoming of regulatory obstacles, the biomaterial can consolidate itself as a sustainable alternative for regenerative medicine and tissue engineering.

Keywords: Biomaterial, Fish Collagen, Biomedical Applications, Integrative Review.

RESUMO
Diante da crescente demanda por biomateriais sustentáveis e seguros, este estudo de revisão integrativa tem por objetivo investigar as aplicações biomédicas do colágeno derivado de peixes, analisando estudos publicados entre 2019 e 2024. As bases de dados PubMed e Web of Science foram pesquisadas, utilizando descritores a partir de DeCS/MeSH (*Fish, Collagen, Potential Biomedical* e *Applications*). A ferramenta Research Rabbits também foi utilizada para auxiliar na seleção de periódicos relevantes. Após a aplicação rigorosa de critérios de inclusão e exclusão, 9 estudos foram selecionados. Os estudos indicam que o colágeno de peixe apresenta promissor potencial com vantagens terapêuticas em relação aos colágenos tradicionais, como menor risco de contaminação e reações alérgicas, incluindo: cicatrização, regeneração tecidual, fabricação de hidrogéis e esponjas de colágeno para aplicações em dispositivos biomédicos. No entanto, permanecem desafios relacionados à padronização dos métodos de extração e à variabilidade entre espécies de peixes. Conclui-se que, com o aperfeiçoamento das técnicas e a superação dos obstáculos regulatórios, o biomaterial

pode consolidar-se como uma alternativa sustentável para a medicina regenerativa e a engenharia de tecidos.

Palavras-chave: Biomaterial, Colágeno de Peixe, Aplicações Biomédicas, Revisão Integrativa.

RESUMEN
Dada la creciente demanda de biomateriales sostenibles y seguros, este estudio de revisión integrativa busca investigar las aplicaciones biomédicas del colágeno derivado de pescado mediante el análisis de estudios publicados entre 2019 y 2024. Se realizaron búsquedas en las bases de datos PubMed y Web of Science utilizando descriptores DeCS/MeSH (Fish, Collagen, Potential Biomedical y Applications). También se utilizó la herramienta Research Rabbits para facilitar la selección de revistas relevantes. Tras una rigurosa aplicación de los criterios de inclusión y exclusión, se seleccionaron 9 estudios. Los estudios indican que el colágeno de pescado tiene un potencial prometedor con ventajas terapéuticas sobre los colágenos tradicionales, como un menor riesgo de contaminación y reacciones alérgicas, incluyendo: cicatrización de heridas, regeneración tisular, fabricación de hidrogeles y esponjas de colágeno para aplicaciones en dispositivos biomédicos. Sin embargo, persisten desafíos relacionados con la estandarización de los métodos de extracción y la variabilidad entre especies de peces. Se concluye que, con la mejora de las técnicas y la superación de los obstáculos regulatorios, el biomaterial puede consolidarse como una alternativa sostenible para la medicina regenerativa y la ingeniería de tejidos.

Palabras clave: Biomaterial, Colágeno de Pescado, Aplicaciones Biomédicas, Revisión Integradora.

1 INTRODUCTION

In recent years, advances in biomaterials have revolutionized the understanding and treatment of health problems by producing and applying artificial or natural materials that interact with biological systems, thereby promoting the restoration, replacement, or improvement of bodily functions. Biomaterials have played an essential role in modern medicine, from the development of orthopedic implants to medical devices such as stents and heart valves. In this context, marine resources, such as fish, emerge as promising alternatives, offering biocompatible, biodegradable, and sustainable materials (Davison-KotleMarshall; García-Gareta, 2019; Aguilar, 2022).

The relevance of using fish collagen becomes even more evident when we consider market trends. The Global Fish Collagen Market is estimated to reach US$6.6 billion by 2025, with consistent annual growth (Avila Rodríguez; Rodríguez Barroso; Sánchez, 2018). These figures reflect the growing interest not only from researchers but also from investors and industry, especially in the cosmetics, nutraceuticals, and medical devices sectors.

Thus, collagen extracted from fish has gained prominence due to its unique properties and wide applications. According to Jafari et al., (2020) collagen is a fundamental structural protein widely used in tissue regeneration, wound healing, and scaffolding. Furthermore, the use of fish-derived collagen contributes to sustainability by reusing byproducts from the fishing industry that would otherwise be discarded, thus reducing waste and minimizing environmental impact (Rojo; Vázquez; San Román, 2014; Jafari et al., 2020).

Fish collagen has a molecular structure with distinct advantages over bovine and porcine collagen, as it offers a lower risk of contamination by diseases transmissible between mammals and the likelihood of allergic reactions (Jafari *et al.*, 2020; Rajabimashhadi *et al.*, 2023). The correlation between the role of collagen in the biomedical context and in cellular and molecular biology can be understood through a more in-depth analysis of the functions and interactions of this protein in biological processes (Yamada et al., 2014; Souza; Castro; Silva, 2021).

Collagen is an essential component of the extracellular matrix (ECM) that provides structural and biochemical support for cells. Collagen's ability to provide this structure also influences cell migration, a process fundamental to embryonic development, wound healing, and immune responses (Lodish et al., 2013; Medeiros; Dantas-Filho, 2017).

Thus, by exploring the potential of fish collagen, it is possible to understand how cellular and molecular interactions can be directed towards therapeutic and regenerative applications in the biomedical field and related areas. Gaikwad; Kim, (2024) highlight that, despite the growing interest in fish collagen as a biomedical alternative, there are still significant challenges. The composition and properties of this protein can vary between fish species, which affects its quality and functionality. In addition, extraction

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and purification methods must be optimized to ensure the standardization required for biomedical use. Another relevant point is the sustainable and ethical supply of fish collagen, considering possible environmental and social impacts associated with its production (Gaikwad; Kim, 2024).

In this context, this integrative review article aims to analyze the potential and biomedical applications of fish-derived collagen, based on scientific evidence published between 2019 and May 2024, highlighting its advantages and identifying gaps that can guide new biotechnological studies from the perspective of cellular and molecular biology.

2 METHODOLOGY

This study is characterized as an integrative literature review, as described by Ercole; Melo; Alcoforado, (2014), with the objective of synthesizing the results obtained in research on the biomedical potential and applications of fish-derived collagen in a systematic, orderly, and comprehensive manner. The methodology was structured in five distinct stages:

1. Identifying the Theme and Defining the Guiding Question

   Initially, the research question was defined: "What is the biomedical potential and applications of fish-derived collagen, and how do the molecular and cellular properties of this biomaterial contribute to its effectiveness in the biomedical field? This question guided the entire process of searching for and selecting studies.

2. Research Strategy

   The search strategy was systematized with the definition of databases and keywords, applied in a standardized manner:

- Databases: Studies were searched in the PubMed and Web of Science databases.
- Auxiliary tool: The artificial intelligence tool Research Rabbit (https://www.researchrabbit.ai/) was used to improve the selection of articles and the identification of duplicate publications (Cole; Boutet, 2023).

- Search terms: Descriptors were selected from DeCS and MeSH, using the controlled terms "Fish", "Collagen", "Biomedical Potential", and "Applications". The combination of these terms was performed using the Boolean operator "AND", in the following string: ("Fish"[MeSH] AND "Collagen"[MeSH] AND "Biomedical Potential"[MeSH] AND "Applications"[MeSH]).

3. Establishing Inclusion and Exclusion Criteria

The criteria adopted for inclusion of studies were:

- Publications of original studies in full text, available in open access.
- Studies that experimentally address or present case reports on the potential and applications of collagen derived from fish.
- Articles published in English, in the period between 2019 and 2024.

Studies were excluded if:

- They did not present results directly aligned with the objective of the study.
- They were duplicates, literature reviews, or publications before 2019.

4. Data collection

Two independent reviewers, Ivana Araújo (IA) and Juan Paiva (JP), conducted the search and selection of studies. The process included:

a) Preliminary reading of titles and abstracts for initial screening of articles.

b) Evaluation of the full text of pre-selected articles.

c) Organization of extracted data in tables, where the first table described the title, journal, type of study, and objective, and the second table grouped the studies according to the type of intervention, potential, and applications identified.

d) Resolution of Disagreements:

During the selection, any disagreements between the reviewers were recorded and resolved through joint discussions, using a third evaluator, when necessary, to reach a consensus. This procedure ensured the consistency and replicability of the screening, enabling a rigorously substantiated final selection.

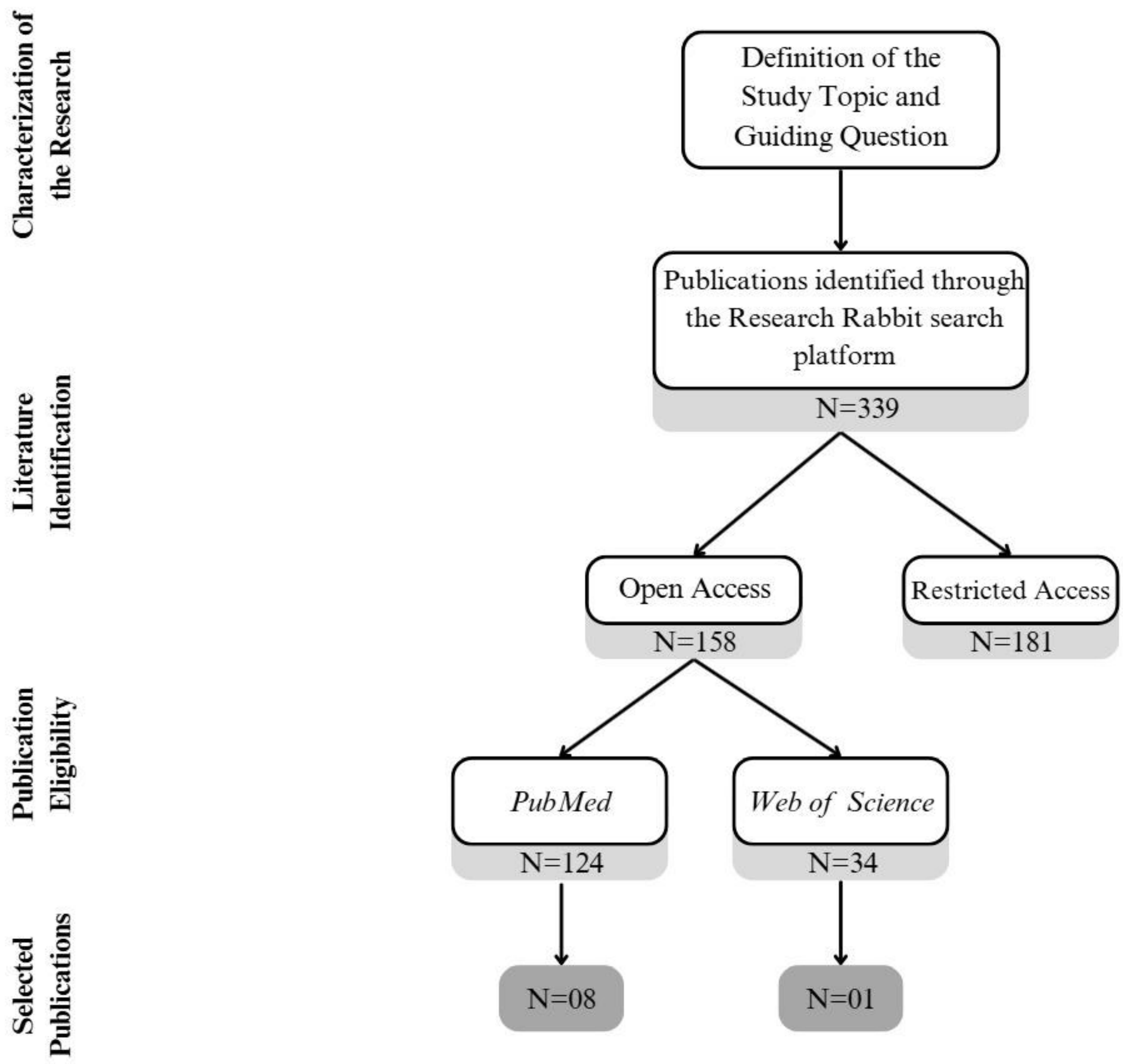
5. Analysis of collected data and presentation of results

After the final selection, the data from the included studies were organized into tables and analyzed qualitatively and quantitatively. The flow of the selection process is presented in a flowchart (Figure 1), which illustrates the reduction in the number of studies from the initial search to the final selection. The analysis focused on identifying the main potential and applications of fish collagen, as well as discussing the technical and regulatory challenges for its clinical and industrial applications.

3 RESULTS

In the initial searches performed in significant journals and repositories, 339 publications were identified. Of these, 181 were excluded due to restricted access. The remaining 158 studies were then analyzed based on their objectives, methods, potential applications, and the biomedical relevance of fish-derived collagen. The identified studies were organized by journal, and 149 were excluded because they did not meet the established inclusion criteria. Consequently, 09 studies were selected, as illustrated in the identification and selection process flowchart (Figure 1).

Figure 1. Flow of the process of identifying and selecting works



Source: Authors

The theoretical framework in a study comprises a critical and organized analysis of the literature relevant to the topic, providing a theoretical contextualization and defining the key concepts. It must comprehensively encompass theories, models, and previous research, identifying gaps, contradictions, and consensus in the literature that are pertinent to the focus of the work being developed.

Table 1: Characteristics of selected studies

Authors	Title	Source	Type of study	Main Objective
(Chen et al., 2019	Fish Collagen Surgical Compress Repairing Characteristics on Wound Healing Process *In Vivo*	Pubmed (Marine drugs)	Experimental	To evaluate the healing potential of tilapia collagen sponges.
(Lima-Junior *et al.*, 2019)	Innovative treatment using tilapia skin as a xenograft for partial thickness burns after a gunpowder explosion	PubMed (Journal of Surgical Case Reports)	Case report	Using tilapia skin as a xenotransplant
(Zhang *et al.*, 2019)	Pepsin-Soluble Collagen from the Skin of *Lophius litulo*: A Preliminary Study Evaluating Physicochemical, Antioxidant, and Wound Healing Properties	Pubmed (Marine drugs)	Experimental	To evaluate the physicochemical properties, antioxidant activity, and the healing potential of collagen from the skin of a specific species of fish.
(Seixas *et al.*, 2020)	Extraction and Characterization of Collagen from Elasmobranch Byproducts for Potential Biomaterial Use	PubMed (Marine drugs)	Experimental	To use cartilage by-products of elasmobranchs (sharks and rays) to extract high-purity collagen for biomedical applications in cartilage regeneration.
(Ge *et al.*, 2020)	Comprehensive Assessment of Nile Tilapia Skin (Oreochromis niloticus) Collagen Hydrogels for Wound Dressings	PubMed (Marine drugs)	Experimental	To evaluate the potential of Nile tilapia skin collagen hydrogels for dressings.
(Kuwahara, 2021)	Extraction of Type I Collagen from Tilapia Scales Using Acetic Acid and Ultrafine Bubbles	Web of Science (Processes)	Experimental	Use Type I collagen, extracted from tilapia scales, in regenerative medicine to provide a sustainable and valuable resource.
(Wu; Yang; Chen, 2022)	Preparation and Characterization of Tilapia Collagen-Thermoplastic Polyurethane Composite Nanofiber Membranes	PubMed (Marine drugs)	Experimental	To develop collagen nanofiber membranes for fibrotic cell growth, with promising mechanical properties and thermal stability for tissue repair.
(Rodrigues *et al.*, 2023)	Potential of Atlantic Codfish (*Gadus morhua*) Skin Collagen for Skincare Biomaterials	PubMed (Molecules)	Experimental	Develop a cod collagen membrane for dressings and skin care.
(Pourjabbar *et al.*, 2023)	Improving the properties of fish skin collagen/silk fibroin dressing by chemical treatment for corneal wound healing	PubMed (International Wound Journal)	Experimental	Improve the properties of a fish skin silk collagen/fibroin dressing through chemical treatment.

Source: Authors

Table 2 presents a summary of the selected studies, highlighting the main potential benefits associated with fish-derived collagen as outlined by the authors. This analysis focuses on three principal axes: type of intervention, potential, and biomedical applications. The data facilitates an investigation into the use of this protein in various areas, highlighting its potential in therapeutic and regenerative applications, while also identifying gaps for future studies.

Table 2. Study selection results

Authors	Type of intervention	Potential	Applications	Identified gaps
(Chen *et al.*, 2019)	Use of tilapia skin collagen to prepare pepsin (PCS) and acid (ACS) soluble sponges.	Tissue healing and regeneration	Treatment of wounds and burns.	Standardization in production processes.
(Lima-Junior *et al.*, 2019)	Xenotransplantation of tilapia skin	Reduction of scarring and inflammation, in addition to a decrease in hospital costs.	Treatment of severe burns	Long-term studies on cell integration.
(Zhang *et al.*, 2019)	Pepsin-solubilized *Lophius litulon* skin collagen (PSC)	Biocompatibility and antioxidant properties	Development of dermatological products and biomedical dressings	Variability of fish species and extraction methods.
(Seixas *et al.*, 2020)	Elasmobranch (shark) collagen and stingray cartilages for hydrogel production	Structural support and stimulation of cell migration	Tissue engineering and bone regeneration	Economic feasibility for production and at scale
(Ge *et al.*, 2020)	Preparation of collagen hydrogels from the skin of Nile tilapia solubilized in acid (ASC) and pepsin (PSC)	Acceleration of wound healing and skin regeneration	Treatment of deep second-degree burns and development of new dressings	Regulation and approval for clinical use
(Kuwahara, 2021)	Type I collagen from tilapia scales, obtained by an ecologically correct method, using aeration of ultrafine bubbles of carbon dioxide gas in an acetic acid solution.	Increased mechanical strength and biocompatibility	Bioengineering for tissue replacement	Development of dermatological products and biomedical dressings, and studies on controlled degradation
(Wu; Yang; Chen, 2022)	Fibrous Thermoplastic Collagen-Polyurethane (Col-TPU) Membranes Prepared	Nanostructure formation with improved structural stability	Tissue regeneration for biomedical implants and prostheses	Clinical studies of long-term cellular interaction

	Using Tilapia Collagen by Electrospinning			
(Rodrigues *et al.*, 2023)	Atlantic cod skin collagen membranes	Dressings and biomaterials for skin care. (better support for adhesion and cell growth)	Biomedical and cosmetic applications	Incorporate other components into collagen to enhance its biological activities, facilitate cell migration assessment, and evaluate its impact on wound closure.
(Pourjabbar *et al.*, 2023)	Use of silk fibroin and fish collagen to form membranes	Improved transparency, mechanical strength, and cell adhesion	Tissue engineering for corneal wound healing	Studies on controlled degradation and cellular response

Source: Authors

4 DISCUSSION

Evidence suggests that fish collagen stands out as an innovative and sustainable alternative for biomaterials, due to its unique composition, rich in glycine, proline, and hydroxyproline, which confers high biocompatibility and efficient interaction with human tissues. These characteristics favor tissue regeneration and effective wound healing, presenting a lower risk of contamination and allergic reactions compared to bovine or porcine collagen, which can raise ethical and health issues (Oslan *et al.*, 2022). In addition, the use of this biomaterial contributes to the valorization of by-products from the fishing industry, promoting a sustainable and environmentally friendly production chain that expands its therapeutic and industrial relevance.

The nine studies analyzed (Tables 1 and 2) consistently demonstrated that fish collagen presents excellent results in various contexts. Collagen sponges (Chen *et al.*, 2019) showed the ability to accelerate healing and promote tissue regeneration. Tilapia skin xenotransplantation (Lima-Junior et al., 2019) demonstrated reduced healing time and decreased inflammation. Pepsinization extraction (Zhang *et al.*, 2019) demonstrated antioxidant properties and high bioactivity.

Furthermore, innovative strategies for the formation of hydrogels (Seixas *et al.*, 2020) and nanofibers (Ge *et al.*, 2020) expand the possibilities of applications in tissue engineering, as discussed by Souza; Castro; Silva, (2021). Interventions involving hybrid biomaterials with polymers (Wu; Yang; Chen, 2022) and applications in cell culture (Rodrigues *et al.*, 2023) demonstrate the versatility of fish collagen, reinforcing its usefulness in tissue repair, but also in the fabrication of advanced biomedical devices.

The study by Pourjabbar et al., (2023) addresses the combined use of fish collagen and silk fibroin to produce ocular dressings, thereby improving transparency, mechanical strength, and cell adhesion — essential characteristics for corneal wound healing. These results signify a substantial advancement in the application of biomaterials for ocular tissue engineering.

Thus, the experimental models and clinical reports analyzed indicate that collagen-derived foams, xenografts, and hydrogels can accelerate healing, facilitate re-epithelialization, and offer structural support for tissue regeneration (Chen et al., 2019; Zhang et al., 2019; Ge et al., 2020; Kuwahara, 2021; Lima-Junior et al., 2019; Pourjabbar et al., 2023; Rodrigues et al., 2023).

This variety of approaches highlights the versatility of fish collagen, suggesting that its applications may range from burn and wound therapies to the development of medical devices and cosmetic products. Thus, in addition to enabling promising therapies, such as effective wound closure and support for tissue reconstruction, fish collagen presents itself as a sustainable alternative, valuing fishing byproducts and reducing the risk of allergic reactions and contamination, which are common in collagens of terrestrial origin.

In addition, other studies highlight the application of this biomaterial in tissue engineering, whether in the form of hydrogels, sponges, or nanofibrous membranes, creating supports that facilitate cell proliferation and differentiation. Initiatives involving hydrogels for bone regeneration, sponges for wound healing, and membranes for ocular tissue engineering underscore the need to diversify extraction and processing methodologies, thereby enhancing the properties of collagen.

However, despite the promising results, challenges remain that need to be overcome to consolidate fish collagen in therapeutic and industrial practice. Notably, the variability in the properties of fish collagen can be influenced by factors such as the species or tissue type, environmental conditions, and the various extraction methods employed.

This variability can impact the structural and mechanical characteristics of the bioproduct, affecting, for example, the bioactivity and reproducibility of the observed results (Souza et al., 2021; Zhang et al., 2019). To reduce these variations, strategies such as ultrasound-assisted extraction, deep eutectic solvents, and pulsed electric field-based processes can be explored. These technologies can reduce the excessive use of reagents, shorten processing time, and enhance the preservation of collagen structure.

Furthermore, the clinical implementation of fish collagen-based products still faces regulatory hurdles. Authorities require robust safety data, long-term efficacy, and standardization in the biomaterial extraction and characterization processes.

In this context, the identified variability and lack of standardized protocols may hinder regulatory approval. Future research should therefore incorporate studies on biocompatibility, toxicity, and cellular integration in both *in vitro* and *in vivo* models. Close collaboration between researchers, industries, and regulatory bodies is essential to establish standards that guarantee the quality and safety of products, thus favoring the transition from the laboratory to practical (clinical) application (Lima-Junior *et al.*, 2019; Pourjabbar *et al.*, 2023).

In summary, the reviewed results reinforce that, despite the therapeutic and industrial benefits already demonstrated, the consolidation of fish collagen in regenerative medicine and tissue engineering will depend on overcoming technical and regulatory challenges. Therefore, future research should prioritize the optimization of extraction processes, the standardization of protocols, and the conduct of in-depth clinical studies to ensure the commercial and medical viability of this innovative and sustainable biomaterial.

5 CONCLUSION

This integrative review demonstrates that fish-derived collagen possesses unique characteristics that qualify it as a promising biomaterial for both clinical and industrial

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applications, highlighting its high biocompatibility and potential in facilitating healing and tissue regeneration processes. Although technological advances have enabled innovative extraction and application methods, challenges related to the standardization of protocols, the variability of properties, and regulatory and economic obstacles still need to be overcome. Future research should focus on optimizing extraction processes and conducting robust clinical studies to consolidate fish collagen as a sustainable and effective alternative in regenerative medicine.

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