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Bioactive collagen peptides: bibliometric approach and market trends for aquatic sources

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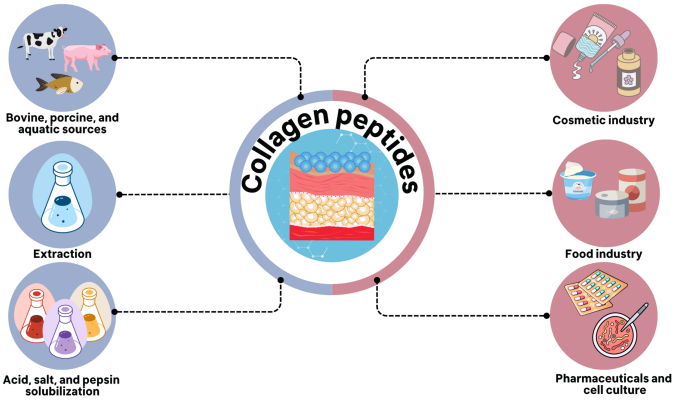
Abstract
The development of the collagen peptides industry is associated with new consumption trends among the population, projected to reach a value of 795 million USD by 2025. Given the relevance of the topic, the present work provides an overview of collagen, its sources, applications, as well as the properties and bioactivities of the peptides formed from its hydrolysis. In addition, a bibliometric analysis was performed to highlight a global overview of publication trends, co-authorship, and co-occurrence of keywords. Bibliometric data were obtained from the Web of Science platform using the descriptors “marine collagen peptide,” “marine collagen peptides,” “aquatic collagen peptide,” “aquatic collagen peptides,” “marine collagen hydrolysate,” “marine collagen hydrolysates,” “aquatic collagen hydrolysate” and “aquatic collagen hydrolysates” and the Boolean operator “OR,” to include terms that cover the possible variations used in the search. From the results obtained, articles and reviews published between 2000 and 2021 were selected. From the analysis of the data collected, it became evident the still relatively recent nature of the research on collagen peptides derived from aquatic organisms and the role of countries in Asia and Europe as leaders in the segment. The co-authorship analysis reveals that the collaboration network between authors/institutions is still scarce and strongly restricted to researchers/institutions in the same region. The co-occurrence analysis reveals that most of the works are related to the health area, highlighting its potential in the prevention/treatment of diseases. In view of the results obtained, it is expected that the growth of the production and commercial branch of these peptides will be accompanied by the amplification of collaboration between authors and institutions from different territories, establishing a global network of partnerships.

Keywords: Aquatic collagen, bioactive hydrolysate, functional foods, by-product processing, bibliometric analysis.

Graphical Abstract



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ROYALDATASET

1. Introduction

Maintaining a healthy lifestyle is essential to prevent and/or treat chronic diseases, such as diabetes, hypertension, and cancer, as well as a series of other inflammatory and autoimmune diseases that limit well-being and threaten the lives of more severely affected patients. Awareness of this fact leads to increased consumer demand for natural and healthy alternatives in the formulation of food products and supplements, pharmaceuticals, nutraceuticals, as well as cosmetic products. In this scenario, collagen-based peptides from sustainable sources emerge as therapeutic agents, and their use on the global market has been increasingly encouraged, mainly due to their numerous beneficial health properties (Ahmed et al., 2020).

The collagen peptide production industry has grown exponentially in the last few years, which is related to new consumption trends within the population. As a result, the growth of the global collagen peptides market is reflected in expressive numbers, having reached the level of US$ 599 million in 2020, with a projected development and reach of the mark of US$ 795 million by 2025, in an expansion that must meet the needs of European, Asian, North, and South American markets (Markets and Markets, 2022).

In the commercial market, the main presentations of collagen peptides are in dry and powdered forms, mainly required by the food and beverage industry, where they are added to their preparations (nutritional supplements and functional foods). In addition, the use of peptides by the pharmaceutical, biomedical, and even cosmetic industries is highlighted, where collagen and its derivatives are the focus of studies related to their properties and applications (Nuñez et al., 2020). One of the ways to map trends within this area of research has been the use of computational tools and software that help group and identify patterns of study of peptides and their applications over time. In this context, the present work aims to conduct a review using bibliometric data about collagen peptides, focusing on new market trends for its aquatic sources.

2. Methodology

The methodological approach was carried out based on two distinct moments of research: (i) research and cataloging of scientific data for the theoretical basis; and (ii) bibliometric survey of scientific data.

(i) Research and cataloging of scientific data:

For the development of this literature review, searches were performed from scientific databases, such as ScienceDirect (https://www.sciencedirect.com/), Elsevier (https://www.elsevier.com/), Scopus (https://www.scopus.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Wiley Online Library (https://onlinelibrary.wiley.com/) and Google Scholar (https://scholar.google.com.br/), using as keywords: “collagen,” “collagen sources,” “aquatic collagen,” “collagen properties,” “collagen extraction,” “collagen hydrolysis,” “collagen peptides,” “collagen bioactive peptides,” “collagen peptides applications.” For that, titles and abstracts were read to select articles, books, book chapters, and scientific notes, excluding those not within the proposal or that did not contain information relevant to the investigation. Publications in English and Portuguese that met the search criteria were included. Thus, a bibliographic review was carried out to compose the theoretical foundation and gather the knowledge currently present in the scientific literature about the properties, sources, and techniques of collagen extraction, as well as the production methods, applications, and bioactivities of the peptides obtained from their hydrolysis.

(ii) Bibliometric approach:

The bibliometric data used in this research were obtained from the Web of Science Core Collection (https://www.webofscience.com/) in the period ranging from 2000 to 2022. The descriptors used in the database were: “marine collagen peptide,” “marine collagen peptides,” “aquatic collagen peptide,” “aquatic collagen peptides,” “marine collagen hydrolysate,” “marine collagen hydrolysates,” “aquatic collagen hydrolysate,” and “aquatic collagen hydrolysates.” All terms were searched in the “topic” field, including titles, abstracts, authors' keywords, and Plus keywords, a database feature that expands the set of keywords related to documents by listing terms frequently cited throughout the works. In addition to keywords, the Boolean operator “OR” was used to include terms that cover the possible variations used by the authors in the search. Based on the results obtained, only

scientific articles and review articles published between 2000 and 2021 were selected since this type of publication provides in-depth scientific data.

The search data (complete record and cited references) were then exported and launched in the bibliometric data analysis software VOSviewer© (version 1.6.17), which can create networks and form data clusters by analyzing the strength of their correlation. Microsoft Excel was also used to organize the data obtained from the research. In the present work, the co-authorship relationships between researchers, organizations, universities, and countries were analyzed in order to identify collaborative networks. Furthermore, the co-occurrence of keywords among works in the area of interest was analyzed to highlight trends within the research field. A summary of the search and obtaining bibliometric data extraction process is illustrated in **Fig. 1**.

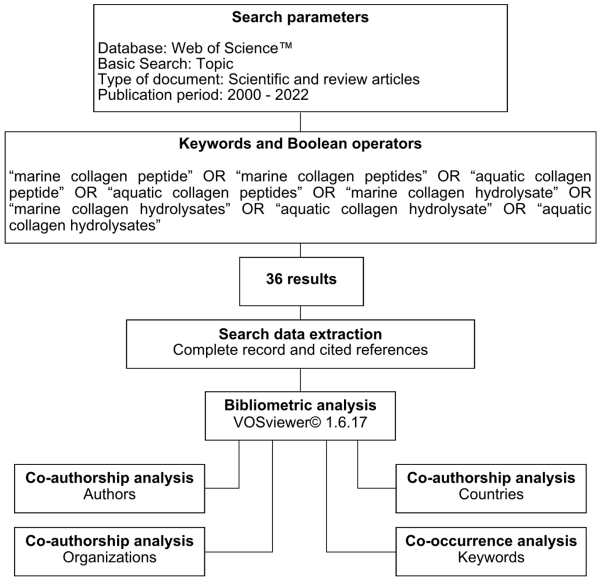

Fig. 1 Flowchart of the process of searching and obtaining the bibliometric data used in the analysis.

3 Results and Discussion

3.1 Collagen: sources, extraction, and properties

Collagen is the most abundant fibrous protein in animals, representing up to 30% of all protein content. Structurally, collagen fibers are presented in the form of a triple helix, formed by 3 subunits coiled around a single axis (Chen et al., 2021). The most traditional sources of collagen are bovine (Nešović et al., 2019), porcine (Zhu et al., 2020), and birds (Hong et al., 2021); however, over the years, the investigation of aquatic sources has advanced (Salvatore et al., 2020). This change is due to the perception of the benefits of these alternative sources, which include biocompatibility and biodegradability, in addition to the particular advantages of aquatic organisms, such as the lack of cultural and religious impediments to their consumption (observed in the consumption of bovine and porcine in some cultures) and the lack of association of aquatic sources with zoonosis transmission, such as bovine spongiform encephalopathy avian flu (Akita et al., 2020).

Marine ecosystems are sources of numerous valuable products, from minerals, fatty acids, and amino acids to bioactive compounds and proteins, such as collagen, a protein of high commercial and biological value (Olatunji, 2020; Dave et al., 2019). Collagen from marine organisms can be extracted from vertebrates such as fish (Shang et al., 2021) and invertebrates such as mollusks, sponges, sea cucumbers, and sea anemones (Li et al., 2020; Ferrario et al., 2017).

The obtaining of collagenous products from aquatic sources is similar to that of terrestrial organisms and can be done using an isolated method or a combination of techniques, using mainly acids, salts, and enzymatic hydrolysis, in addition to more innovative methods, such as the use of ultrasound (**Fig. 2**). Equally relevant, the pre-treatment of the material is a crucial step, which consists of removing impurities (non-collagenous proteins, fatty material, debris, and dirt), in addition to reducing the size of the samples, increasing the contact of the parts with the extraction solutions (Ahmed et al., 2020), which can improve the yield of the raw material (Oliveira et al., 2021).

Collagen extraction is performed using various techniques, with equally variable methodologies and advantages/disadvantages as following described. (1) Acid solubilization is based on the collagen property of being more soluble in acid than in water. In this way, the acidic solution increases the repulsion between the tropocollagen molecules, leading to their solubilization. This type of collagen is known as Acid Soluble Collagen (ASC) (Ahmed et al., 2020). (2) Another method used is enzymatic hydrolysis, which is generally used alone and/or in conjunction with the acid method in order to increase the final yield of the extraction. In this method, the enzymes used the most are pepsin, papain, and collagenase, the former being the most used in the treatment of fishing residues (Li et al.,

2020). (3) The salt solubilization method, although less necessary (lower solubility of collagen in salt medium and, consequently, lower yield), can also be used. This technique usually uses sodium chloride (NaCl) solutions (Oliveira et al., 2021).

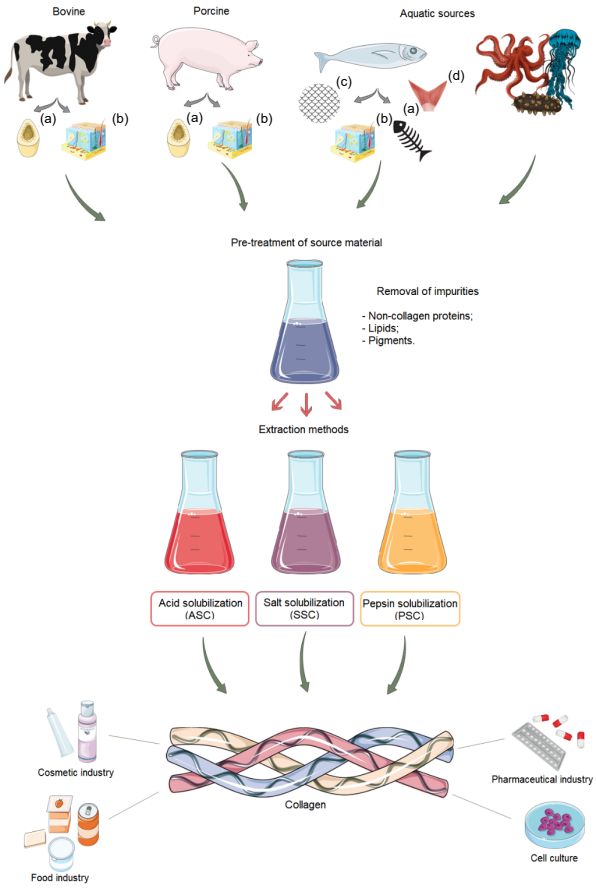

Fig. 2 Major sources and collagen extraction methods employed by the global protein market. (a) Bones; (b) skin; (c) scales; (d) fins. Source: Produced with the aid of SMART – Servier Medical Art.

New approaches have emerged to assist and optimize already established extraction methods, reducing time and/or energy consumption and the need for reagents during this process, such as ultrasonication (Ali et al., 2018), electrodialysis (Chen et al., 2019), isoelectric precipitation (Lin et al., 2019) and extrusion-hydro-extraction (Huang et al., 2016), all of which have already been successfully used in collagen extraction processes of aquatic origin in different areas of biotechnology.

3.2 Aquatic collagen peptides: bioactivities

Biochemically, low molecular weight peptides are identified through short sequences (about 2-20 amino acids) resulting from protein cleavage by protease (Chen et al., 2021). Although derived from more complex proteins, peptides have biological properties distinct from those of the native molecule and each other. Collagen peptides are known in the scientific literature for their bioactivities, such as antioxidant (Chen et al., 2018), antihypertensive (Chen et al., 2021), iron chelating (Luo et al., 2020), wound healing (Lakra et al., 2022), antimicrobial (Ahmed & Chun, 2018) and antiadipogenic (Lee et al., 2017), serving different segments such as the pharmaceutical, cosmetic, biomedical and food industries. These sectors formulate beneficial and safe products using such properties due to their biocompatibility, low allergenicity, and degradability. In addition, due to their low molar mass, collagen peptides are easily digested and absorbed by the animal organism (Nuñez et al., 2020).

3.2.1 Antioxidant activity

Antioxidants are active compounds that protect cells from the harmful effects of free radicals in order to avoid oxidative stress by interrupting the chain of oxidative reactions within cells (Wei et al., 2021). Reactive oxygen species (ROS) or “free radicals” are highly reactive chemical forms formed during oxygen metabolism, including hydroxyl radicals (OH), superoxide anion radicals (O^{2-}), hydrogen peroxide (H_2O_2), peroxyl radicals (ROOH), and nitroxide radicals (NO) (Wu et al., 2018). Although the occurrence of these species is natural, their generation can also be exacerbated by external factors linked to lifestyles, such as exposure to solar radiation, pollution, and harmful chemicals, which cause oxidative stress (excessive production of free radicals) and, consequently, damage to genetic material, proteins, and lipids, among other physiological damages, such as premature aging, the development of inflammatory, neurodegenerative, cardiovascular diseases, weakening of the immune system, diabetes, and tumors (Sierra et al., 2021).

Among the best-known antioxidant compounds are substances such as carotenoid pigments (lycopene, β-carotenes), vitamin C, and vitamin E (Nirmala et al., 2018), present in various foods such as salmon, shrimp, and yellowish/reddish vegetables (peppers, for example), in addition to citrus fruits (Zhang et al., 2018). Supplementation of food with synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tert-butylhydroquinone (TBHQ), and propyl gallate (PG) is commonly administered by the

industry in order to minimize food oxidation and potential toxicity (Falowo et al., 2014). However, the consumption of these synthetic substances can have adverse health effects, requiring strict control over the use of these artificial products (Pan et al., 2016).

Due to the harmful consequences associated with synthetic antioxidants, the industrial segment has been increasingly engaged in research for natural alternatives that can perform as antioxidants without loss of effectiveness compared to traditional options. Among these, collagen peptides have been successful in removing free radicals from the body (preventing the oxidation of polyunsaturated lipids in the cell membrane), regulating the levels of these reactive species, and assisting the physiological defense system (Song et al., 2021; Wu et al., 2018). The diversity of aquatic-derived sources of collagen peptides with antioxidant activity currently being studied is exemplified in **Table 1**.

Table 1 Collagen peptides derived from aquatic organisms with antioxidant activity.

Species	Residue	Hydrolysis method	Molecular weight	Technique	Ref.
Chanos chanos	Scales	Pepsin	< 3 kDa	DPPH assay; ABTS assay	Chen et al. (2018)
Salmo salar	Skin	Protease from *Vibrio* sp.	< 3 kDa	DPPH assay	Wu et al. (2018)
Thunnus obesus	Skin	Static hydrothermal hydrolysis	< 1 kDa	ABTS assay	Park & Jo (2019)
Rhincodon typus	Cartilage	Termolisine	37 kDa	DPPH assay	Jeevithan et al. (2015)
Raja clavata	Muscle	Protease, alcalase, neutrase	85-3500 Da	DPPH assay	Lassoued et al. (2015)
***Oreochromis* sp.**	Scales	Alcalase, Flavourzyme	*	ABTS assay	Sierra-Lopera and Zapata-Montoya (2021)
Beringraja pulchra	Cartilage	Trypsin; Quimotripsin; Papain	< 3 kDa	DPPH assay; ABTS assay	Li et al. (2021)
Penaeus notialis	*	Pancreatic trypsin	150-550 Da	DPPH assay	Montero et al. (2019)
Loligo vulgaris	Skin	Alcalase	1–10 kDa	ABTS assay	Nakchum and Kim (2016)

*Information not provided by the authors.

3.2.2 Iron chelating

Iron is one of the most significant minerals present in animal organisms. Essential for maintaining biological functions such as hematopoiesis, carrying oxygen through the blood, and maintaining healthy hemoglobin levels, beyond being a vital component for enzymes crucial for cellular metabolism and neural and immune systems functions (Lin et al., 2021). Currently, iron deficiency is the most frequent “hidden hunger” (Masuda et al., 2020), which means that among the micronutrients (vitamins and minerals), iron presents the highest deficiency rate in the world population. A deficit like this is closely related to injuries like anemia, metabolism and cognitive development harm, and increased infant and maternal mortality. Worldwide, about 20% of people suffer from anemia related to iron deficiency, with children between 0-5 years old, women of childbearing age, and the elderly being the most affected population (Zhang et al., 2021).

In fact, only the iron consumed in food is insufficient to meet the body's demand. In order to fight iron deficiency and its associated risks, different types of supplements have been developed over time (Wu et al., 2020). In this sense, the first initiative involved developing and administering ferrous salts. However, this formulation has been disused due to lower bioavailability and consequent lower absorption rate (Zhang et al., 2021). Aiming to solve the problem, new supplement formulations have included amino acid-ferrous ion complexes, increasing the absorption rate. However, using amino acids makes production more expensive and propitious to lipid oxidation and loss of food color (Lin et al., 2021; Luo et al., 2020).

Recently, food fortification with ferrous peptide-ion complexes has shown to be more advantageous due to its better stability, safety, absorption, and bioavailability than previous supplements. These advantages promote iron transport and absorption by the intestine from the peptide absorption mechanisms (Luo et al., 2020). In addition, fish skins and scales of different species have been investigated in search of more efficient and cheaper protein sources. Some of these species include Nile tilapia (*Oreochromis niloticus*) (Lin et al., 2021), Alaska pollock (*Theragra chalcogramma*) (Guo et al., 2015), and milkfish (*Chanos chanos*) (Huang et al., 2015).

3.2.3 Wound healing

The skin is the largest organ in the human body and has attributes for its maintenance, including sensory function and its role as the first physical barrier between an organism and the environment. However, as a covering organ, the skin is constantly in contact with harmful substances, pathogens, and various pollutants. Therefore, these are considered common risks whose exposure enables the

introduction of pathogens that can jeopardize the well-being and even the individual's life (Moholkar et al., 2021).

Morphologically, mammal skin comprises three layers, as highlighted in the sequence. 1) Epidermis: the most superficial layer, rich in keratin (95%); 2) dermis: medium layer, rich in collagen (70%); 3) hypodermis: deeper layer, composed of loose connective tissue and fat (Mayet et al., 2014). Depending on the depth of the layer affected by the lesion (cut, burn, laceration), the healing process involves different stages (inflammation, cell proliferation, tissue remodeling), which become increasingly complex, dynamic, and especially time-consuming (Moholkar et al., 2021).

The long time taken for the physiological regeneration of skin tissue integrity should be considered a key factor that can make patients more susceptible to complications, the most common being the risk of infections (Mihai et al., 2019). Therefore, traditionally, the treatment of skin lesions relies heavily on the administration of oral and topical antibiotics, which, although consistent, causes discomfort for the patient, in addition to adding the risk of developing resistance to these drugs, which is especially harmful for those patients with chronic injuries who need prolonged treatment (Han & Ceilley, 2017). In this way, the search for alternatives is encouraged to increase the well-being of individuals, as well as minimize risks and accelerate the healing process.

The development of dressings is a topic of great interest in the fields of medicine and pharmacology, and, over time, different natural polymers such as alginate (Varaprasad et al., 2020), chitosan (Nešović et al., 2019), silk (Patil et al., 2020), hyaluronic acid (Graça et al., 2020) and collagen (Das et al., 2019) have been proposed as viable materials for dressing composition and tissue engineering. Among these, collagen stands out as one of the most attractive, as in addition to having good compatibility, it also has low antigenicity compared to other biopolymers (Lin et al., 2019). Thus, formulations such as hydrogels, sponges, films, membranes, and collagen-based fibers are extensively studied and applied, ensuring adequate permeability (allowing gas exchange), antimicrobial protection, and acceleration of healing without the presence of cytotoxic effects (Moholkar et al., 2021).

From the successful experience using collagen as an ally in wound protection and acceleration of the healing process (Lakra et al., 2022), the peptides obtained through its hydrolysis also arouse interest regarding their healing potential, as well as their possible courses of action. Unlike collagen's characteristic tough structure, peptides can be more easily digested, absorbed, and transported throughout the body, reaching their target and performing their bioactivity more specifically (Lin et al., 2021). When in contact with a skin lesion, peptides signal a false collagen degradation, which stimulates fibroblasts to synthesize more collagen, essential in tissue remodeling and re-epithelialization processes during healing (Felician et al., 2019). This evidence clarifies the potential of these hydrolysates as significant agents in treating injuries, minimizing consequent risks, and improving patients' quality of life. Examples of aquatic collagen sources recently studied to obtain peptides with healing activity are shown in **Table 2**.

Table 2 Collagen peptides derived from aquatic organisms with wound-healing properties.

Species	Residue	Hydrolysis method	Molecular weight	Technique	Ref.
Oreochromis niloticus	Skin	Digestion by *Clostridium histolyticum*	960–1970 Da	Cell proliferation assay	Felician et al. (2019)
Theragra chalcogramma	Skin	Alcalase	430–1000 Da	*In vivo* experiment using Sprague-Dawley rats	Yang et al. (2018)
Rhopilema esculentum	*	Collagenase II, papain, and alkaline proteinase	< 25 kDa	Cell migration analysis	Shang et al. (2021)

*Information not provided by the authors.

3.2.4 Antimicrobial activity

Microbial resistance to conventional antibiotics is identified by the World Health Organization (WHO) as one of the main threats to public health, derived from a long history of indiscriminate use of these drugs within healthcare systems, in agricultural production and the food industry, and by general populations (Luong et al., 2020). Furthermore, infections with antibiotic-resistant bacteria cause about 700,000 deaths worldwide every year, and it is estimated that this number could reach up to 10 million deaths annually by 2050 (Pfalzgraff et al., 2018), raising questions about a possible “post-antibiotic era” due to the loss of efficacy of these drugs (Kwon & Powderly, 2021).

The most common antimicrobial agents can be grouped into distinct categories based on their

mechanism of action: (1) cell wall synthesis inhibitors; (2) cell membrane depolarizers; (3) protein synthesis inhibitors; (4) nucleic acid synthesis inhibitors; and (5) disruptors of metabolic pathways (Reygaert, 2018). However, despite the wide variety of drugs available, the indiscriminate administration of such drugs is largely responsible for the growing microbial resistance issue. To avoid increasing the severity of the problem, several efforts were launched in an attempt to restrict access to antibiotics; however, only controlling the use of existing drugs is not enough (Tang et al., 2015), making it necessary to develop new drugs to fight infections. In this context, antimicrobial peptides are proposed as a new order of broad-spectrum agents against antibiotic-resistant organisms, with antimicrobial action pathways different from traditional drugs, in addition to inhibiting the formation of biofilms and inducing the dissolution of biofilms already formed (Souza et al., 2022; Wang et al., 2021; Lázár et al., 2018).

The activity of antimicrobial peptides is known to be due to their adhesion to the plasmatic membrane and consequent disruption of target cells (Abdillahi et al., 2018). However, different models of specific pathways are proposed, the most common being the “carpet” and the “detergent” models. In the first model, the peptides tend to cluster and coat the surface of the bacterial membrane, interfering with the stability of the lipid bilayer and increasing its permeability. In the second model, with an increasing concentration of peptides in the membrane, their permeabilization and disintegration intensify, leading to the formation of micelles, as observed in the action of detergents (Wimley, 2010).

From the perspective of using antimicrobial peptides to treat infections, peptides from aquatic sources represent a highly viable and efficient option, as demonstrated in studies that evaluated the antimicrobial activity of peptides produced from tuna (*Thunnus obesus*) (Ahmed & Chun, 2018), and giant squid (*Dosidicus gigas*) skins and even wastewater from cooking anchovies (*Engraulis japonicus*) (Tang et al., 2015) (**Table 3**).

Table 3 Collagen peptides derived from aquatic organisms with antimicrobial activity.

Species	Residue	Hydrolysis method	Molecular weight	Technique	Ref.
Thunnus obesus	Skin	Subcritical hydrolysis	< 600 Da	Agar diffusion disk assay	Ahmed and Chun (2018)
Dosidicus gigas	Skin	Pepsin, alcalase and esperase	≤ 75 kDa	ABTS assay; RP-HPLC; Agar diffusion disk assay	Mosquera et al. (2014)
Engraulis japonicus	Cooking residual water	Protamex	1104 Da	Microbroth dilution analysis	Tang et al. (2015)

*Information not provided by the authors.

3.2.5 Anti-adipogenic activity

Obesity is a complex pathological metabolic condition, often associated with changes in the functional and morphological characteristics of adipocytes, which is manifested in the excessive accumulation of white adipose tissue (Ahn et al., 2022). Currently, obesity is considered an epidemic, with its prevalence tripling in recent decades and approaching a rate of 20% of the global population (Gómez et al., 2021). This increase is especially concerning given the condition's connection with other chronic diseases such as diabetes, hypertension, cardiovascular disease, cancer, and inflammation.

Adipogenesis is a multifactorial process that requires the sequential and orderly activation of two main adipogenic transcription factors: the peroxisome proliferator-activated receptor-γ (PPAR-γ) and the CCAAT/enhancer binding proteins (C/EBPs) (Ahn et al., 2022). By regulating the expression of target genes, such factors stimulate adipocyte differentiation and maintenance. In turn, larger and greater adipocytes lead to a higher accumulation of lipids and the release of pro-inflammatory cytokines and adipokines, generating the risks associated with obesity (Fuggetta et al., 2019). The investigation of collagen peptides from aquatic sources as anti-adipogenic agents is still recent; however, the results obtained so far help to elucidate the role of collagen peptides within the complex mechanism of adipogenesis and how these compounds can serve as adjuvant treatments in treating obesity and improving the quality of life of patients (Lee et al., 2017).

Tests performed with rats fed high-fat diets concluded that ingesting collagen peptides represses the expression of genes responsible for C/EBPs and PPAR-γ in the adipocytes differentiation phase. This effect results in a decrease in the size and proliferation of adipocytes and a reduction in weight gain in animals subjected to the test, regardless of diet, in addition to helping to reduce total cholesterol and triglycerides (Lee et al., 2017). Another relevant

factor for the complexity of obesity pathology is the constitution of the intestinal microbiota. The administration of these peptides also has beneficial effects on restoring the healthy intestinal microbiota of animals, decreasing the incidence of inflammation-causing bacteria, a condition prevalent among obese patients (Wang et al., 2021). Thus, through the progression of studies on the interaction of collagen peptides and different factors influencing the development of obesity, more alternatives for treating this condition are being proposed.

3.3 Market trends and bibliometric approach

The volume of scientific production on the use of biologically active peptides has increased. Knowing, mapping, and filtering information according to industrial interest has become another great challenge. Despite being a relatively recent initiative, bibliometric analysis has proved to be a rich opportunity for study by investigating emerging trends within a scientific area, as well as examining the cumulative scientific production of countries, institutions, and authors on the topic of interest (Donthu et al., 2021), through a quantitative and qualitative analysis of the available literature. In fact, bibliometric analyses have already been carried out in different fields, including the areas of digital marketing (Faruk et al., 2021), economics (Murdayanti & Khan, 2021), education (Behl et al., 2022), and even biotechnology (Mörschbächer & Granada, 2022; Gonçalves et al., 2019), which highlights their versatility. However, to date, there are still no scientific reports of bibliometric analysis to assess the current state and trends of research within the field of peptides, emphasizing those obtained from collagen from aquatic sources.

3.3.1 Bibliometric analysis

From the search focusing on the bibliometric analysis, 36 documents were selected, 33 (96.1%) scientific articles and 3 (8.33%) review articles. Although the search conditions allowed the inclusion of documents published since 2000, the results demonstrate that using aquatic sources to obtain collagen peptides is a recent topic of investigation, whose first publications were dated in 2010 (6 publications) (**Fig. 3**).

After 2010, the variation in the number of publications in the area is remarkable, with a sharp drop in the following years and the reestablishment of a higher number of publications in the years 2020 and 2021, with 5 publications each.

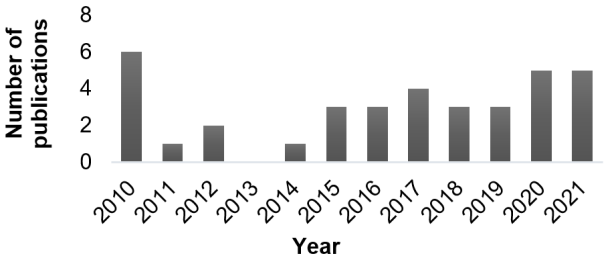

Fig. 3 The number of scientific articles published on aquatic collagen peptides per year. Source: Web of Science Core Collection (Clarivate, 2023).

By observing the geographic distribution of the selected publications, 14 countries participated in the specific literature available on the topic (**Fig. 4**).

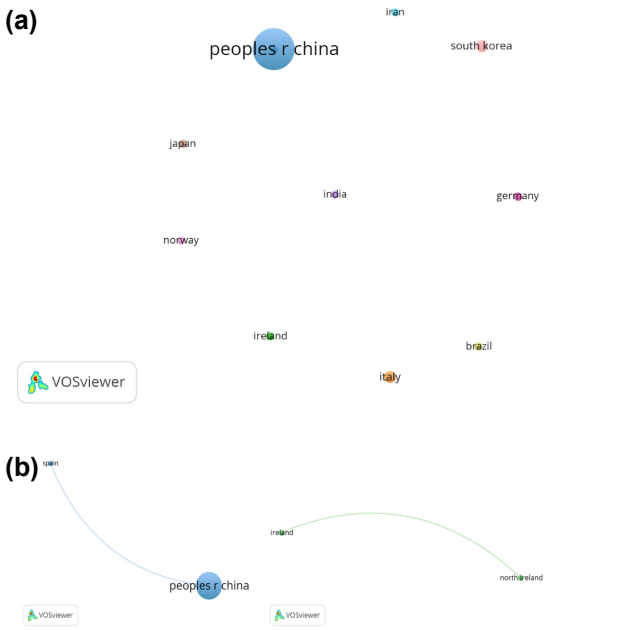

Fig. 4. Countries with contributions to the specific literature on aquatic collagen peptides (a) and Asian and European countries that have established partnerships in their publications (b). Source: Web of Science Core Collection (Clarivate, 2023).

Furthermore, the dominance of Asian and European countries in this field of investigation is confirmed, which is justified by their wide market for this type of product (Mordor Intelligence, 2022). Of the 36 selected documents, 25 (69.4%) were published by authors from China, while countries such as Italy, South Korea, Germany, Japan, India, Iran, Greece, and Brazil have more discreet participation in the total number of publications.

The clusters formed by the *VOSviewer* software from the research bibliometric data confirm

this trend, in addition to demonstrating collaboration patterns among countries. In **Fig. 4a**, the countries with the highest representation in research on aquatic-derived collagen peptides are listed. The size of the circles is proportional to the number of publications in each territory, and the lines represent a collaborative relationship between countries.

From the clusters obtained, it is clear that a strong network of collaboration between countries has not been established yet. The literature shows that even in collaborative work, such partnerships still tend to be carried out between institutions/researchers within the same territory/region (Jiang et al., 2020). The software also allows for an approximation of the image, where it is possible to observe discreet collaborations between China and Spain and between Ireland and Northern Ireland (**Fig. 4b**), further reinforcing the Asian/European hegemony in this field of investigation.

As predicted by the prevalence of studies from the Chinese territory, when highlighting the main organizations active in research on the production and application of collagen peptides, we visualize that among the 53 organizations listed, Chinese institutions are the great leaders in the area, especially the University of Beijing (15 documents, 376 citations) and other higher education institutions and medical and technological research institutes in the country (**Fig. 5**).

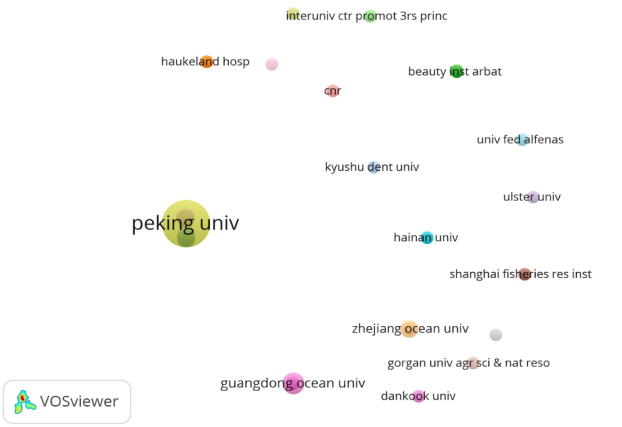

Fig. 5. Organizations with the most publications on aquatic collagen peptides. Source: Web of Science Core Collection (Clarivate, 2023).

With the most robust output among all listed organizations, Beijing University also has the highest number of collaborations with other institutions, especially the Shandong Academy of Medicine and Science and Beijing University of Science and Technology. In the Brazilian scenario, 2 federal academic centers, the Federal University of Viçosa (UFV) and the Federal University of Alfenas (UNIFAL), are listed, with 1 document each.

The co-authorship analysis allows the elucidation of the collaboration degree between different authors. In the present research, without any restriction on the minimum number of publications, a total of 156 authors were listed and distributed in 24 different groups.

In **Fig. 6**, the separation between research groups from different countries is clear, reinforcing the fragility still present in international collaboration networks between researchers within the aquatic collagen peptides research area, with some isolated groups of European researchers and others of Asian researchers, the latter being responsible for the largest co-authorship network within the area.

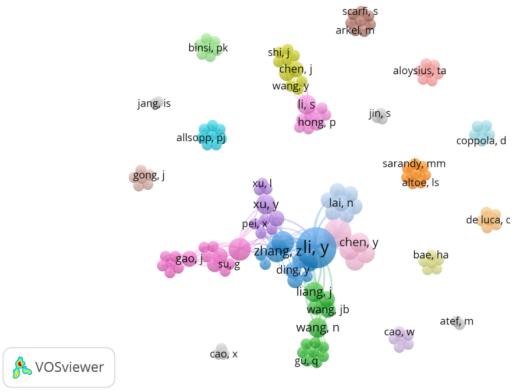

Fig. 6. Overview of co-authorship between researchers from publications on aquatic collagen peptides. Source: Web of Science Core Collection (Clarivate, 2023).

Restricting the search to those authors with more than 4 publications, we obtained 5 main names: Li Y., Zhang F., Wang J., Zhang Z., and Zhao M. All the main authors in the area are present in the largest cluster illustrated in **Fig. 6** and have a close partnership relationship with each other.

The analysis of keywords co-occurrence is relevant to indicate the main thematic points in the research area of interest. In addition, this type of investigation is also capable of pointing out possible research trends (Bretas & Alon, 2021). However, restricting the research to a high minimum number of occurrences adds a temporal limitation to the results since innovative investigations may not yet have a significant contingent of published works. Therefore, the search included terms that occurred at least two times among the selected documents, so more recent

and less represented research initiatives were included.

Furthermore, in order to elucidate the trajectory of research trends within the theme over time, the "overlay" visualization mode was selected. In this type of visualization, the circles and darker lines represent the keywords present in the older works, that is, the most traditionally explored subjects. Meanwhile, the lighter circles and lines represent the most recently used keywords, the topics that have only been studied frequently in recent years. The network that resulted from the selection is represented in **Fig. 7**.

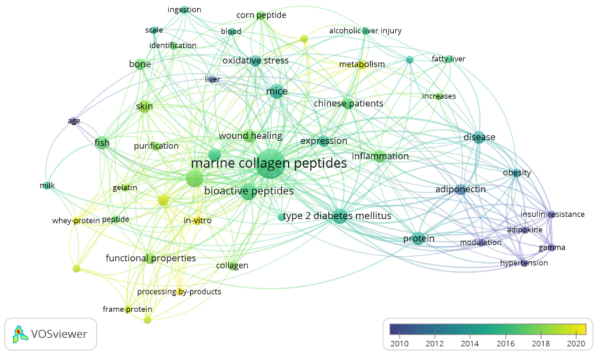

Fig. 7. Network of keywords relevant to the topic (overlay representation) from publications on aquatic collagen peptides. Source: Web of Science Core Collection (Clarivate, 2023).

As can be seen in the image, terms related to antihypertensive, anti-adipogenic activities, and the control of type 2 diabetes have been used since the beginning of publications on aquatic collagen peptides. Over the years, other bioactivities have become more studied, such as anti-inflammatory, antioxidant, and wound healing activities, as well as exploring different sources to obtain collagen, such as skin, bones, and fish scales. Among the most recently used keywords (in yellow) is the term "processing by-product," whose use has been a growing trend in research in recent years (Zamorano-Apodaca et al., 2020).

Fishing industry by-products are excellent sources of collagen. Of all fish caught worldwide, about 25% are converted into by-products commonly discarded after processing (FAO, 2018). The fish filleting process, specifically, turns about 70% of the total weight of fish into waste that is not intended for consumption, such as viscera, bones, skin, scales, and head, causing environmental impact and waste of raw materials rich in biomolecules (Välimaa et al., 2019). In this context, in recent years, these residues have been targets of interest in terms of their potential as a source of biomolecules of interest for several industrial segments, such as collagen, whose hydrolysis results in the production of several bioactive peptides that can be used in beneficial formulations for human and animal health and well-being (Nurilmala et al., 2021).

Table 4 Companies operating in the global collagen peptides market.

Company	Country	Area/Product
Tessenderlo Group® (www.tessenderlo.com)	Belgium	Food for pets and aquatic animals
Gelita AG® (www.gelita.com/en/products-and-brands)	Germany	Food supplements; pharmaceutical products; animal feed; specialties (lubricants, detergents, etc.)
Darling Ingredients® (www.darlingii.com/)	USA	Nutraceutical supplements aimed at strengthening bones and joints and improving the texture and overall appearance of the skin
Holista CollTech® (www.holistaco.com/our-products.html)	Australia	Food supplements to strengthen bones; functional foods and beverages; cosmetics (lotions, face masks, hair products)
Nitta Gelatin® (wellnex-collagen.com/)	Japan	Food supplements; functional foods and beverages; cosmeceuticals; nutricosmetics.
Collagen Solution® (www.collagensolutions.com/)	United Kingdom	Materials for medical use (solutions, powder) and tissue engineering
Amicogen Inc. ® (amicogen.com/en/)	South Korea	Supplements intended for personal care/beauty

From the bibliometric analysis, the leading role of Asian and European countries in peptides from aquatic organisms was evident due to their geographical location. The populations of Asian countries close to the Pacific Ocean have a long tradition of consuming aquatic animals, establishing the consumption of these foods as significant cultural elements (Lipoeto et al., 2012) and making the fishing industry in these regions increasingly profitable. **Table 4** shows the commercial breadth of the collagen peptides branch, as well as their applications.

The high productivity of this industry is linked to the high availability of its by-products, which, together with the available technology, makes these territories great producers of collagen peptides. The

regions with the highest production and market for collagen peptides dictate global trends for this segment. Asian, European, and North American consumers have shown a growing interest in ethically sourced nutraceuticals, supplements, and fortified foods, which has led to the development of products that use fish skin collagen and other fish waste as sources (Global Market Insights, 2022).

When evaluating companies that use aquatic organisms to obtain peptides, the following stand out: Capsugel Belgium NV, GELITA AG, Amicogen Inc., Nitta Gelatin, In., Norland Products, Inc., Vivesa Holding S.R.O., Rousselot and Hangzhou Nutrition Biotechnology Co., Ltd. The increase in life expectancy and the consequent aging of the population is also a factor that contributes to the increase and maintenance of high demand for this type of product. Linked to this, the use of fish collagen peptides as a safer option compared to terrestrial animal derivatives in cosmetic and beautification industry formulations is notable due to their anti-aging and moisturizing functionalities (Zhao et al., 2021). Thus, the growth of the pharmaceutical, nutraceutical, and cosmetic industries worldwide tends to equally stimulate the fish collagen peptides market (Park & Jo, 2019), signaling the importance of this product in the global economy.

4 Conclusions

Given the points addressed in this review and bibliometric study, the importance of research on the production, applications, and current global market of collagen peptides derived from aquatic organisms is evident, considering that it is a relatively new and constantly expanding segment. From the bibliometric data analyzed, the role of Asian and European territories in the global production and commercialization of collagen peptides of aquatic origin is unquestionable due to these territories' access to investments in the area, which guarantee access to the most advanced technologies available. Furthermore, collaborations between research groups and institutions are still limited to researchers from the same or neighboring countries. Therefore, expanding the studies on aquatic peptides must be accompanied by establishing a global collaboration network between researchers. Still, bibliometric analysis, such as the one in the present work, is constantly needed to follow up on changes in the scenario that involves the study and the market of aquatic collagen peptides over time.

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Authors' Contributions
B.A.M.C.: Data Curation, Writing - Original Draft preparation A.L.F.P: Supervision V.M.O: Writing - Review & Editing, Supervision T.S.P: Writing - Review & Editing, Supervision, Project administration. All authors read and approved the final manuscript.

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Informed Consent Statement
Not applicable.

Conflicts of Interest
The authors declare that they have no conflict of interest.

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