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Review Article

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Fish Residue Valorisation by the Production of Value-Added Compounds Towards a Sustainable Zero Waste Industry: A Critical Review

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Abstract Currently, several relevant industries incorporate bioactive fish molecules (proteins, lipids to minerals) in numerous products. The low prices and high quality of the raw material determine the use of these biomolecules. The high demand for fish originates an inadequate overexploitation of marine resources. In most cases, an industry-only uses part of the fish while the rest is discarded. Fish resources are finite and it is necessary to valorise all biomass in a sustainable way. The amounts of under-utilized residues generated by fish processing industries can create serious environmental problems and have led researchers and industries to actively seek for alternative strategies where the residues from fish transformation can be used as raw materials. The biorefinery concept in the search for sustainability is thriving with the use of all substrate to obtain products to be used by different industries whilst single product extraction ceases. Research has been focused on the use of innovative, economically and environmentally sustainable extraction methods to preserve the biological activity of the molecules and respond to the increasing awareness of consumers in product related issues. These pioneer methods can transform fish wastes into added-value by-products using an efficient and viable economic strategy.

In this review, the extraction of different fish residues with environmentally friendly techniques for the obtention of different bioactive compounds will be addressed. The use of different residues and techniques to extract highly desirable biologically active compounds such as collagen, gelatin, lipids, and minerals will be reviewed, demonstrating the potentiality of this subject. The main goal of this review is to help researchers, policymakers and economic agents to understand the trends and the tools available to address such a relevant topic in the years to come.

Keywords fish residues, supercritical fluid extraction, enzymatic extraction, blue economy, circular economy

1. Introduction

The Food and Agriculture Organization (FAO) report, entitled The State of World Fisheries and Aquaculture, states that in 2014 the world fish marine capture was roughly 93.4 million tonnes. The comparison of this data with the corresponding figures for 2013 and 2012 shows an increase in the activity (91.3 and 92.7 million tonnes, respectively). The rapid growth of the world population, predicted to reach 9.5 billion by 2050 from the 7 billion inhabitants reported in 2011, will lead inevitably to an increasing demand for fish. The rapid increase in population allied to the captured fish stocks, which have been increasing unsustainably since 1990, is leading to a high concern about fish stocks and the future of fish capture [1]. Since this is a limited resource, it is important to ensure the correct renovation and conservation of the world fish stocks. Due to this new problematic, new alternatives are now being explored. One of the employed strategies to achieve this goal is to obtain more fish for consumption through aquaculture, thus decreasing marine catch. Another strategy is to forbid the catch of some endangered fish species for a determined period of time if their population is

decreasing [2]. It is important to maintain healthy fish stocks with minimal ecosystem impacts. While in the majority of countries there is a tendency to decrease fish catching and to increase the value obtained from each individual, in developing and highly populated countries-China, Indonesia, India, Russia and Myanmar, the opposite happens. For example, in Myanmar, marine fishing increased by 157% when compared to 2001 [3]. In the European Union, each government institute individual fishing quotas (IFQs) or individual transferable quotas (ITQs) that can be purchased by the fishermen, which determines the quantity of fish they are allowed to catch on the European seas [4]. When the TACs reach their maximum amount no more fishing is allowed. The conservation of the marine species is a distress for most world countries. Therefore, some international treaties have been signed among some countries. It is significant to distinguish another two important treaties that aim the protection of the vulnerable marine ecosystems in the Pacific Ocean: one for the South (The Convention on the Conservation and Management of the High Seas Fishery Resources in the South Pacific Ocean), signed in 2009 and another for the North region in 2012 (Conservation and Management of High Seas Fisheries Resources in the North Pacific Ocean).

Throughout recent years, several industries have shifted their attention to fish as a source of biologically active molecules in addition to the fish processing industry [5, 6]. The high interest of these industries, coupled to the capture of fish for human consumption, leads to an exhaustive exploitation of the marine habitat [7]. Since fish resources are limited due to the constraints caused by regulatory agencies, the high demand for this substrate results in a competition among industries.

The desired molecules are frequently located in different fish parts, and only a small part of the fish is used. Consequently, vast amounts of waste can be produced. As previously mentioned, fishing is determined by quotas and the competition between all these industries may result in not having enough fish to satisfy all the demands. Therefore, it becomes necessary to exploit marine resources in a responsible approach by all the interested parts and force the dialogue between complementary economic activities (Fig. 1).

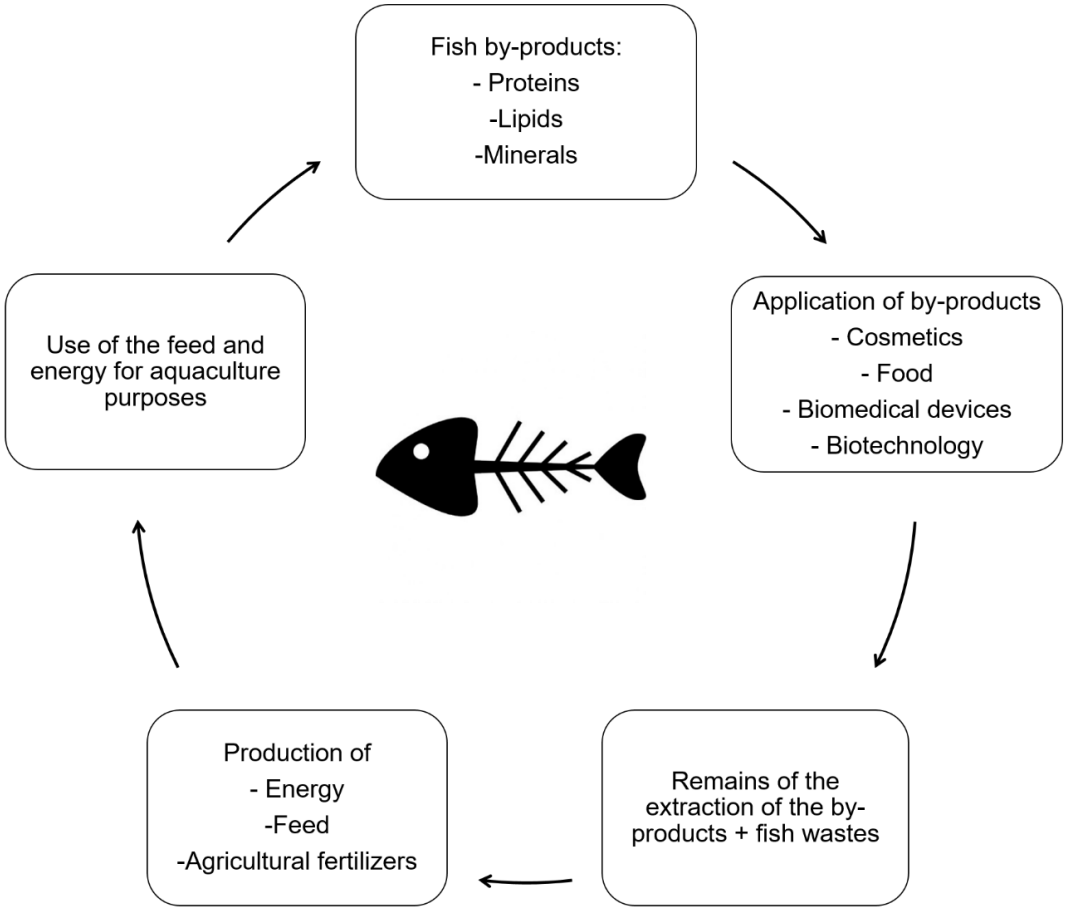

Figure 1: Depiction for the complete use of fish by-products in a biorefinery concept

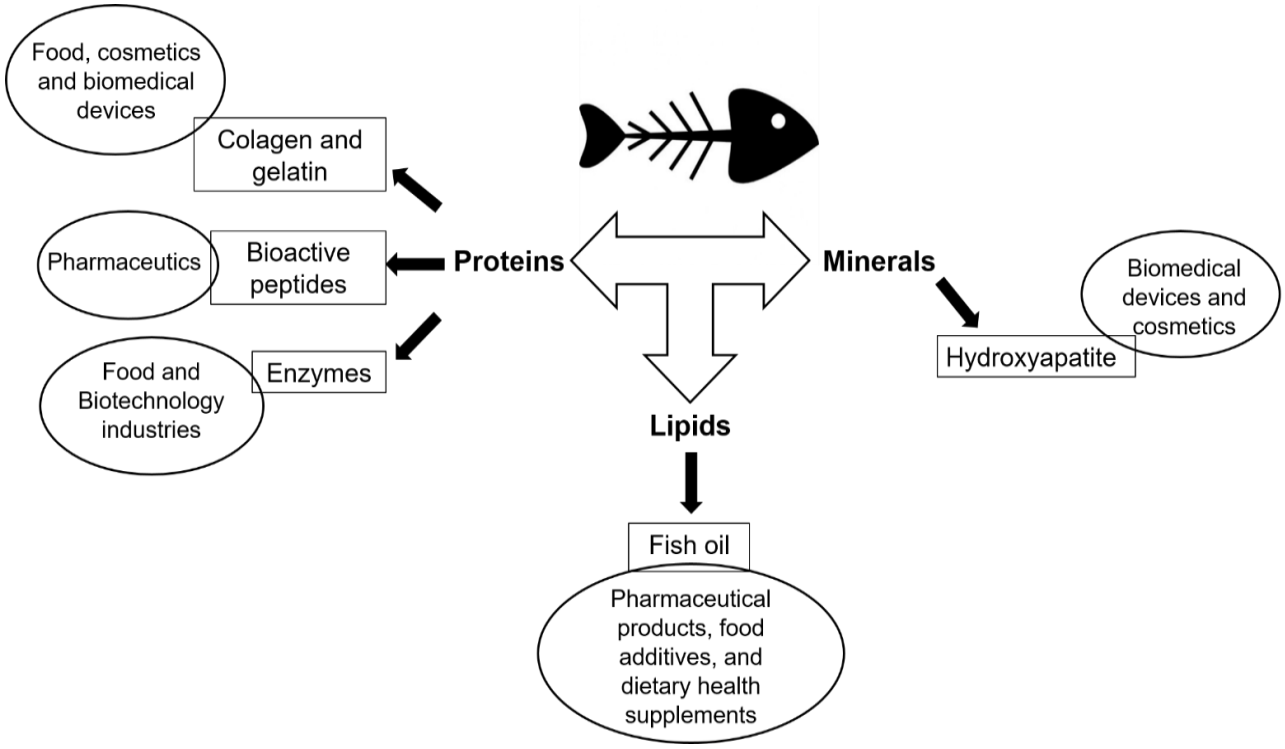

Figure 2: Bioactive molecules extracted from fish and their respective applications in food, pharmaceutical, cosmetics, biotechnology industries and medical devices.

It is reported that from the 93.4 million tonnes fished, about 55% were processed by the fish processing industry for human consumption [1]. After being processed for food purposes, the remaining parts are usually discarded leaving a substantial parcel of its value to explore. Reports show that the fish processing industry produces between 20 to 80% of wastes depending on the fish type and the level of processing [3]. The high organic content of these wastes made it necessary to treat them before being discarded. The initial response of the fish processing industry was to transform the residues to increase their economic viability. Traditionally, fish wastes would be converted into feed for fish, fish oil, pet food or fish silage [8]. To satisfy the rising demand for fish related compounds, attempts were made to use the fish residues as raw materials, thus replacing the need for additional fish catching. The focus is to obtain biologically active compounds for specific industries. An example of fish by-products processors into value-added products are Copalis and Bioceval. Copalis produces fishmeal, fish protein hydrolysates and more recently fractionate and isolate peptides. Bioceval produces fishmeal, fish oil for aquaculture and high-value marine proteins [9].

The presence of some valuable molecules entails the potentiality to apply biotechnological methodologies to this biomass to recover value-added compounds [3, 10, 11]. Several extraction methods were tested and can be used to extract, separate and isolate biologically active molecules of interest [12, 13]. Therefore, the economic value of the fish industry by-products increases, turning this substrate into a more attractive source to explore. From a different perspective, companies that utilize the residues in an eco-efficient process show a socially responsible behaviour allied to the minimization of environmental pollution.

The organic content of fish wastes depends on the type of species, gender, age, their nutritional status, health and time of the year. In average, fish are composed of 15-30% proteins, 0-25% fat and 50-80% moisture [3]. Fish residues consist of solid and liquid matter. The solid wastes are constituted by heads, non-filet flesh, tails, skin, gills gut or viscera's, fins and bones, while the liquid wastes are blood and water [10].

The first reported studies of fish residue extraction revealed its potential through the obtention of innumerable biologically active compounds belonging to several important chemical families.These wastes were found to contain very important protein and lipid fractions besides other potentially interesting compounds. They contain the highly sought omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA),

enzymes (pepsin, trypsin, chymotrypsin), collagen and fatty acids [5, 14, 15]. The bones, besides containing collagen and gelatin, were also found to possess minerals as hydroxyapatiteconstituted by calcium phosphate [16]. Nevertheless, to be able to fulfill this goal the whole fish needs to arrive in perfect hygienic conditions to be processed, separated and then distributed among all the possible production lines (Fig. 2).

This review will comprise the latest research performed in this field with particular attention to environmentally friendly extraction techniques/processes and on the compounds that have been reported, namely proteins, lipids, and minerals.

The methods used for this review article had a base methodology of a direct contact with industries for a clear identification of the issues and the opportunities. A patent search was also performed in several databases (Google patents, PATENTSCOPE WIPO, EPO Espacenet) as patents are very relevant in this field since an economic problem is addressed. As a final step in this review, the information was collected from scientific databases such as Scopus, ScienceDirect, Pubmed, PLOS, Google Scholar and SciELO.

2. Proteins

2.1. Fish muscle proteins

Fish muscle protein's content ranges between 13-24% depending on fish species, age, gender and nutritional conditions [17]. Layers of muscles are disposed on both sides of fish bodies from head to tail and are connected by less connective tissue than terrestrial animals, due to their different methods of locomotion. Their aminoacid composition is similar to terrestrial animals, however, their adaptation to the marine environment led to structurally different proteins with distinct biochemical properties being more susceptible to temperature and pH changes [18]. For example, proteins of cold water fishes are more susceptible to temperature degradation than the ones of in warm habitats. The proteins present in the fish muscle are 70-80% of structural proteins, 20-30% sarcoplasmatic proteins with 2-3% insoluble connective proteins, such as collagen. The majority of structural proteins (66-77%) are myofibrillar comprising 50-60% myosin and 15-30% actin [3]. They are responsible for the contraction and distention of the fish muscles, and consequently for the fish movement. Sarcoplasmatic and insoluble connective proteins when partially hydrolysed may produce highly valuable products that constitute the bioactive peptides that will be further discussed.

2.2. Collagen and gelatin extraction

Collagen is a fibrous connective-tissue protein [19] present in the extracellular space of bones, skins, tendons, cartilage and muscle [20]. It is the most abundant single protein present in fish [21], corresponding to 25% of total proteins in the vertebrates [22], [23], [24]. The structure of the collagen is stabilized by the amount of proline and hydroxyproline present in the molecule, and the amount of these iminoacids provides thermal stability to the protein [25]. The iminoacid content depends on the type of collagen, their location, and function. Due to the fact that fish inhabit in colder habitats, fish collagen possesses less amount of proline and hydroxyproline when compared to mammals collagen [26].

Several types of collagen have been identified and classified according to their primary structures or forms of supramolecular organization [27, 28]. The types of collagen also differ by their fibrillary structure and degree of cross-linking [29], and their structure depends on the function that they perform in the body. The predominant type of collagen in fish is type I, which has three equal α chains. Nevertheless, type II or III with different α chains have also been found in shark cartilage [24]. For example, Type V was isolated from fish intramuscular connective tissue [30], and it is a heterotrimer constituted by two or three different α chains [31]. Type I is the most common form found in the connective tissues, like skin, muscle, bones. Research shows that in some fish species (saury, carp and chum salmon) the most common type I occurred, whereas in others (eel and common mackerel) a new variation exists formed by three different types of polypeptide chains ($\alpha_1\alpha_2\alpha_3$) [32]. Collagen provides mechanical support to the connective tissues, being the most abundant macromolecule of the extracellular matrix involved in tissue development, remodelling and repair by providing essential architectural support and affinity-driven regulation of key signalling cascades [33]. As a material, it is biodegradable with weak antigenicity and high biocompatibility, which are excellent properties to be employed in food, cosmetics and biomedical devices [34]. Collagen can be produced transgenically from plants (for instance, tobacco plant)

[33]. However, this collagen may be biologically inactive when used in cosmetics, so attempts have been made to isolate animal-produced collagen [35].

Collagen extraction can be performed either by chemical (acid) or enzymatic hydrolysis. It is important to choose a suitable extraction method taking into consideration the potential application since the extraction methodology influences the lengths of the polypeptide chains, as well as, its physical-chemical and functional properties [36]. Chemical hydrolysis is commonly used in industries since it is a cheaper process when compared to the enzymatic hydrolysis. Nevertheless, this last process provides a higher nutritional product with improved functionality [37]. A general extraction procedure for collagen is shown in Fig 3.

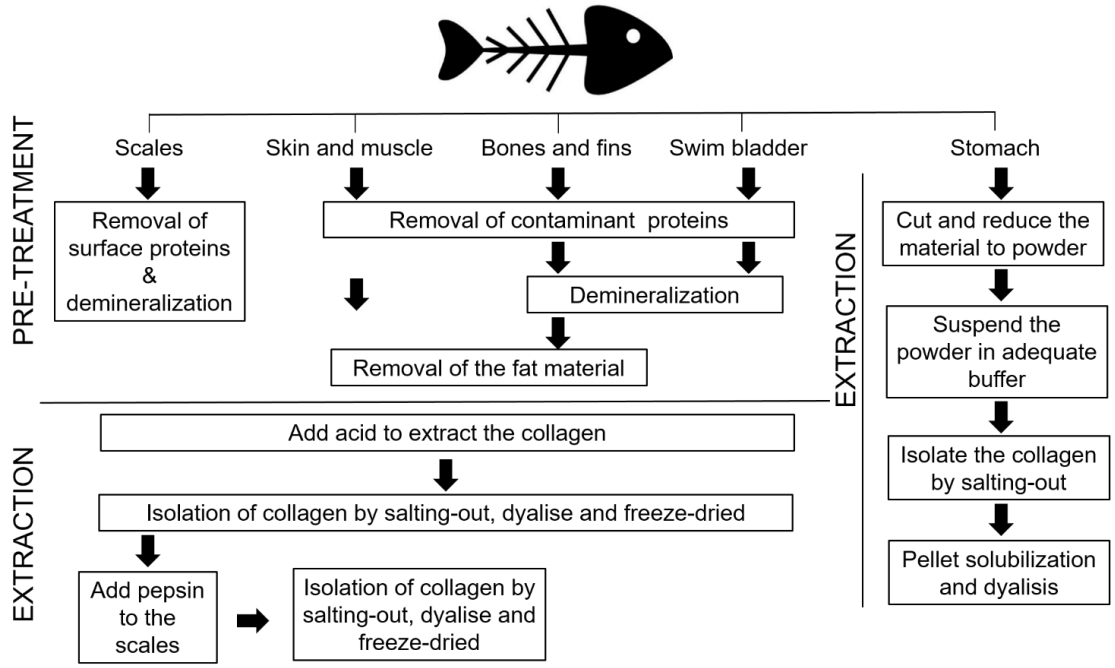

Figure 3: General scheme of the isolation procedures used to extract collagen from different origins on fish wastes

The first step is to remove the protein covalent intra and intermolecular cross-links [23]. Given the chemical nature of the collagen and its presence in different fish parts, different extraction approaches can be applied (Fig. 3). When a chemical approach is employed, a pre-treatment with an acidic or basic solution and with organic solvents, depending on the origin of the raw material, is performed to increase the yield and to remove non-collagenous substances such as proteins, pigments, minerals, and fat [38]. Normally, an acidic pre-treatment is performed in soft tissues, as skin, muscles, while a basic is applied to harder tissues, such as bones. The skin, muscle, bones, and fins usually need an additional treatment with organic solvents to remove the fat. In the particular case of extracting collagen from scales, bone, fin and swim bladderit is necessary to use an EDTA solution to demineralize the substrate and afterward perform the collagen extraction from the mineral particles. An enzymatic approach can also be applied to perform the necessary pre-treatment to remove other proteins present as contaminants [23].

Once the pre-treatment is performed, the substrate needs to be filtrated to remove the insoluble alkali elements. In all, the resultant protein solution is dissolved in an acetic solution, filtered and then the collagen is salted out by the addition of a base, dialysed to remove the salts and additional contaminants (small molecules) and freeze dried [24]. Ideally, the extraction of collagen needs to be performed at lower temperatures employing enzymatic techniques, mostly proteases capable of breaking the bonds that link this protein with the other molecules of the substrate. For instance, collagen extraction using pepsin enzyme was obtained from the skin of blue shark (*Prionace glauca*), small-spotted catshark (*Scyliorhinus canicula*), yellowfin tuna (*Thunnus albacares*) and swordfish (*Xiphias gladius*). This resulted in type I collagen with antioxidant capacity [39]. Nonetheless, other

variations have been performed in several fish species targeting mainly the removal of other proteins or contaminants, such as fats and pigments [40–44] and different types of raw material [45–48].

The collagen extraction can also be accomplished by enzymatic methods using proteases that cleave the chemical bonds, preferably the telopeptide part of the protein. Usually, this procedure is carried out in acidic medium due to a more efficient solubilisation of the collagen, and a single or a set of enzymes can be used [49–51]. The use of commercial enzymes was already applied with great success. Nevertheless to overcome the industrial constraint that enzyme prices may cause the use of enzymes from natural sources was also studied, thus potentially increasing industrial competitiveness. For example, a patent has been filled in which the collagen was extractedfrom the skin of aquatic fishes using a protease isolated from papaya (papain) [52]. On the other hand**,** digestive fish proteins have also been successfully employed in the extraction of collagen and gelatin [47, 53]. More recently, deep eutectic solvents (DESs) have been successfully used for collagen extraction. Under the studied conditions, both high and low molecular weight collagen was obtained with high yields [54]. The latest research in this field has followed different approaches: the study of the physicochemical properties of the different isolated collagen molecules [55–61]; the isolation and characterization of the isolated protein [56, 57, 62–67]; the use of ionic liquid to extract the collagen protein from fish scales [68]; the construction of a collagen film from the skin of shark catfish [69] and the sequential extraction of collagen and collagen hydrolysates by enzymatic hydrolysis [70].

Gelatin is collagen's hydrolysed form obtained by heat denaturation [5]. Gelatin shares some of the collagen's properties since their aminoacid composition is similar. Additionally, it has the capacity to absorb water, to form a gel and to stabilize emulsions [23]. The standard method to extract gelatin involves a pre-treatment that could be acidic or basic depending on the raw material, a thermal extraction and a purification step [36]. The pre-treatment for both collagen and gelatin is similar. However, unlike the collagen extraction that produces several collagen types, only two types of gelatin are obtained. Gelatin type A is obtained with acid hydrolysis and type B with basic hydrolysis [71]. Fish skins are the main source of gelatin [72–77], although it can be also extracted from bones and scales [78]. The type of gelatin and purity depends on the extraction method used. New methods have been developed to achieve gelatine with good stability to be used in food formulations, as reported by Ketnawa, with the use of a peptidase from fish viscera [79] or with the use of a commercial enzyme such as pepsin [74]. However, most of the methods employed nowadays by the industry are conventional ones with slight modifications on the pre-treatment, such as prolonged alkali treatment during 6-14 days [80]. More recently, the research on gelatin extraction methods has been focused on the gelation properties when different extraction methods are employed [77, 81],on the addition of gelatin, extracted from Tilapia in three stage processes, to yogurts and acidic milks [82] and on the relation of decreased gelatin dissolution with the formation of cross-links between amino acids [83].

2.3. Collagen and gelatin applications

Collagen and gelatin have many industrial applications. Due to their intrinsic properties, they are both widely used in cosmetics, pharmaceutical, biomedical devices, and food. Type I collagen has been used in regenerative medicine [84, 85]. It is an inert supported tissue (well tolerated by the body) used in scaffolds, chemically stable when combined with other compounds and best suited for the new field of tissue regeneration for repairing and regenerating tissue and organs. Additionally, it is a support matrix that allows the restoration, structuration, and function of injured connective tissue [86]. Other applications of collagen are: paste for soft-tissue augmentation [87, 88], low-porosity sheets to act as adhesion barriers [89–91], scaffold for meniscal repair [92, 93], bone tissue engineering [94, 95] and dura substitute [96], implant device materials [97–99], collagen shields in ophthalmology [100], sponges for burns/wounds [101] mini-pellets and tablets for protein delivery [102],and gel formulation, in combination with liposomes, for sustained drug delivery due to his inherent biointeractive properties [103–105].

Gelatin properties and characteristics are defined by the collagen from which it is originated, i.e., the amino and iminoacid constitution. At room temperatures, gelatin has the capacity to rearrange and stabilize its tridimensional structure forming a gel. Thus, it can be used to improve elasticity, consistency, and stability of foods, as well as, to produce edible and biodegradable films that increase the shelf life of a food product [106].

Gelatin can also be applied in either soft or hard capsules to be used in food and pharmaceutical industry due to its elasticity and robustness [107]. It also plays a role in the medical field, due its biodegradability, non-toxicity, its ability to crosslink and to modify chemically. These partially hydrolysed proteins are, as well, promising candidates as a source of nanomaterials for carrying drugs, due to its lack of immunogenicity [108, 109]. The application of these proteins depends on the quality of the extracted products and on the preservation of its biological activity. The obtention of a very pure protein is an adamant condition to reduce the risk of an allergic reaction when applied in medical devices [110]. Other examples of recent collagen and gelatin applications are reported in Table 1.

Table 1: Potential applications of collagen isolated from fish in different fields

Article	Authors & Year	Ambition
Food and Beverage		
The functional properties and application of gelatin derived from the skin of channel catfish (Ictalurus punctatus)	[111]	Demonstration of the potential of channel catfish gelatin in ice-cream and beer for higher emulsion capacity, stability and higher foaming stability than calf bone gelatin leading in the future for its substitution
Evaluation of tilapia skin gelatin as a mammalian gelatin replacer in acid milk gels and low-fat stirred yoghurt	[82]	Demonstration of the potential of tilapia skin gelatin to replace mammalian gelatin in yoghurt
Nano-liposomal entrapment of bioactive peptidic fraction from fish gelatin hydrolysate	[112]	Encapsulation of bioactive fish gelatin peptide fraction into a nanoliposome as a source of direct application of these antioxidant peptides in foodstuffs that may exhibit an alternative to overcome the issues associated with the direct application of antioxidant peptides in food
Physico-chemical characteristics and fibril-forming capacity of carp swim bladder collagens and exploration of their potential bioactive peptides by in silico approaches	[113]	Obtention and characterization of type I collagen from carp swim bladder. The obtained carp collagens were reported to release several bioactive peptides and potentially could be used as functional ingredients in food industries
Isolation, characterization and valorizable applications of fish scale collagen in food and agriculture industries	[114]	Isolation of acid-soluble collagen from scarp scales to produce a milk-based food product incorporating the extracted collagen to be applied as an economic source of nitrogen fertilizers for plants
Physical and oxidative stability of fish oil-in-water emulsions stabilized with fish protein hydrolysates	[115]	Evaluation of fish protein hydrolysates of sardine and small-spotted cat shark muscle proteins as

		protein emulsifiers for the production of oxidatively stable fish oil-in-water emulsions to incorporate fish oil into liquid foods protect fish oil against oxidation in the food system
	Packaging	
Effects of pH modification in proteins from fish (Whitemouth croaker) and their application in food packaging films	[116]	Development of films for food packaging by using modified proteins by thermal or pH-induced denaturation to improve food packaging from sustainable sources so that this material is used for commercial uses
Composite bioactive films based on smooth-hound viscera proteins and gelatin: Physicochemical characterization and antioxidant properties	[117]	Development of composite films additive with peptides or polysaccharides to improve antioxidant properties to use as bioactive packaging material in order to decrease the use of synthetic packaging, responsible for several ecological problems due to their non-biodegradability
Production and assessment of Pacific hake (Merluccius productus) hydrolysates as cryoprotectants for frozen fish mince	[118]	Production of fish protein hydrolysates by enzymatic methodology as a viable alternative to the sugar-based cryoprotectants currently used for frozen fish products.
Physicochemical properties, antimicrobial activity and oil release of fish gelatin films incorporated with cinnamon essential oil	[119]	Incorporation of cinnamon essential oil into fish gelatin film with improved characteristics to be used as an active food packaging to replace synthetic antimicrobials
Edible film with antioxidant capacity based on salmon gelatin and boldine	[120]	Obtention of edible films of salmon gelatin, boldine, and sorbitol with a potential application on extending the shelf life of fresh food products such as meat, fish or cheese in order to substitute current synthetic polymers
Thermo-mechanical, rheological, structural and antimicrobial properties of bionanocomposite films based on fish skin gelatin and silver-copper	[121]	Application of nanocomposite films based on fish skin gelatin as an active food packaging materials for food preservation by controlling

nanoparticles		foodborne pathogens and spoilage bacteria.
	Medical Devices	
Fabrication of an ultrafine fish gelatin nanofibrous web from an aqueous solution by electrospinning	[122]	Preparation of an ultrafine fish gelatin nanofibrous web by electrospinning without any additive polymers or temperature control facilities and evaluation based on a cell proliferation study by culturing human dermal fibroblasts, being an alternative to mammalian gelatin
Ultra-thin hydro-films based on lactose-crosslinked fish gelatin for wound healing applications	[123]	Development and characterization of an ultra-thin hydro-film based on lactose-mediated crosslinking of fish gelatin by Maillard reaction and demonstration of suitable properties for biomedical applications. This could be readily applied to replace synthetic hydrogels that do not possess the intrinsic ability to support tissue organization
Immunological effects of collagen and collagen peptide from blue shark cartilage on 6T-CEM cells	[124]	Assessment of the physicochemical and in vitro mechanism of immunologic tolerance of pepsin-soluble collagen and its peptide from blue shark cartilage. This study revealed the potentiality of shark cartilage peptides to be a nutraceutical.
Soft nanocomposites of gelatin and poly(3-hydroxybutyrate) nanoparticles for dual drug release	[125]	Demonstration of the potential of sustainable soft nanocomposites with tilapia fish skin gelatin as an injectable co-sustained drug release system, which could solve the issue of the increasing lack of solubility of most drug candidates being discovered
Bioavailability of angiotensin I-converting enzyme (ACE) inhibitory peptides derived from Virgibacillus halodenitrificans SK1-3-7 proteinases hydrolyzed tilapia muscle proteins	[126]	Evaluation of tilapia muscle fractions protein hydrolysates potential bioavailability for the inhibition of the angiotensin I-converting enzyme

Collagen/chitosan porous bone tissue engineering composite scaffold incorporated with Ginseng compound K	[95]	Preparation and characterization of fish scale collagen with ginseng compound K scaffold materials with biocompatible and supported the growth cells for bone regeneration

2.4.

2.5. Bioactive peptides

Bioactive peptides consist of 3–20 amino acids [127] that are naturally present in the fish or incorporated into their proteins [128]. They can have a positive impact on the body functions and may even influence health [129, 130]. Peptides are inactive within the proteins and become active after being released by digestion and absorption; *in vitro* enzymatic hydrolysis or fermentation. These protein fragments are found in all parts of the fish mostly in their hydrolysates [131]. These peptides are antihypertensive, antioxidative, immunomodulatory, prebiotic, mineral binding, antithrombotic and hypocholesterolemic [132]. Recently, the anti-proliferative property of fish hydrolysates added a new value to these peptides [133, 134]. Their nutritional value is a function of their aminoacid contents and their properties depend on a set of variables such as hydrolysis time, temperature, enzyme/substrate ratio, pH and pre-treatment [135, 136]. Marine peptides are particularly interesting because fish are composed mainly of structural, myofibrillar and sarcoplasmic proteins that have all the essential aminoacids, predominantly lysine, phenylalanine and valine [137]. These aminoacids are essential and need to be ingested since the human body cannot synthesize them. Traditionally the used extraction method is enzymatic hydrolysis to obtain a crude hydrolysate. Then peptides are separated according to their sizes followed by peptide isolation and protein sequencing. Lastly, a synthetic peptide is assembled and the bioactivity is tested [138].

Due to their properties and characteristics, marine peptides can have pharmaceutical and medical applications. The large utilization of oxygen in all our body's functions makes us vulnerable to oxidative damages. The potential role of oxidative stress in several diseases has been thoroughly reviewed, as for example cardiovascular diseases [139], diabetes [140], cancer [141], neurodegenerativedisorders [142] and ageing [143].

The potential applications of marine peptides have been widely researched. Certain marine peptides may play a role in inhibiting the angiotensin-converting enzyme (ACE). ACE increases the blood pressure by constricting the blood vessels and certain marine peptides have been found out to be antihypertensive [144]. This inhibitory aspect has been reported to be linked to the presence and sequence of certain aminoacids present in marine peptides [145]. There are reports that peptides originated from the hydrolysis of marine collagen prevent photoaging, which increases their applicability in cosmetics and medicine [146]. The advantage of using marine peptides is that they exhibit high activity with potentially no secondary effects [147, 148]. These peptides display immunomodulatory and anti-microbial activities. Albeit their immunomodulatory activity is relatively unspecific, studies revealed that some marine peptide extracts showed growth inhibition of the herpesvirus [149],enhancement of the interleukin 2 (IL2), molecules responsible for the activation of leukocytes in HIV patients [150] and promote the capacity of lymphocytes to proliferate in response to an immunological stimulus of the T-cells [151].As marine peptides possess antioxidative, immunomodulatory and antihypertensive properties [152], they can take part in the functional foods, food supplements, cosmetics and pharmaceutical products. An example is the obtained hydrolysates of red *Tilapia* treated with alcalase and thermolysin that showed antioxidant and antihypertensive activity [153]. In another application, cod hydrolysates obtained by fermentation with a proteolytic Bacillus strain originated several peptides ranging from1.4-3 kDa with antihypertensive properties [154]. In another study, a low-molecular peptide fraction with ACE-inhibitory activity encapsulated into fish gelatin nanovesicles showed to be functionally active. Moreover,the capsulation process did not affect its function [155]. More recently, the skin hydrolysates of *Prionace glauca*, *Scyliorhinus canicula*, *Xiphias gladius*, and *Thunnus albacores* was subjected to enzymatic hydrolysis and resulted in collagen peptides with anti-oxidant activity [39]. Bioactive peptides from sardinella muscle proteins have been described by Jemil et al and the authors report that this hydrolysate is a good source of natural antibacterial, antioxidant and antihypertensive peptides [156]. The potential of using biopolymer-coated nanoliposomes as a carrier of rainbow trout skin-derived antioxidant peptides was also recently verified [157]. Although there have

been numerous studies, as shown previously, it is important to discover new marine peptides from other marine sources, to conduct studies using appropriate models that mimic the biological structure and ideally perform *in vivo* studies.

2.5. Fish enzymes

Enzymes are proteins or polypeptides that are used to catalyse or accelerate chemical reactions. The fish internal organs, viscera, heads, skin and bones area good source of marine enzymes [158]. Proteases, lipases, and transglutaminases are the most common enzymes found in fish. Some marine enzymes are unique while others are equal to the ones found in terrestrial animals. Nevertheless, marine enzymes possess new characteristics. For example, proteases with high catalytic activity at a relatively low concentration [159, 160].Generally, these fish enzymes possess a high tolerance to salt, adapt to cold temperatures, remain stable at high temperatures and their production is easy to scale up [161]. Two different review papers discuss the potential of these enzymes in biocatalysis. Trincone gathered the information available on enzymes of marine origin and highlighted that the specific features of their habitat (salt tolerance, hyperthermo stability, barophilicity, cold adaptivity, etc) lead to their unique specificity and affinity to the substrate-linked with their metabolic functions. He also described novel chemical and stereochemical properties, especially in oxidoreductases and carbohydrate active enzymes, which can be used to face environmental pollution. Another interesting enzyme mentioned in this review is a lipid hydrolase that acts in wax esters in cold environment or the epoxide hydrolase that produces a diol with specific stereochemistry, which is an important chemical reaction used in drugs production [162]. Trincone also described the novel chemistry and stereochemistry diversity of these new marine biocatalystshighlighting their application in the pharmaceutical and chemistry area. Due to all the advantages presented by the marine enzyme, several patents were submitted between 1973 and 2007 [163]. All of them in five domains of application, most in the chemistry and pharmacological areas. The application in these two areas resides in the unique stereochemical characteristics of these marine biocatalysts [164]. However, these enzymes possess some drawbacks that concern their limited availability, the instability of the raw material, the limited bioavailability depending on the extraction methods and the quality of the wastes/residues [165]. Due to their specific traits, marine enzymes are commonly usedin enzymatic extraction and preferably employed by the food industry [5]. Traditional methods of extraction depend on the part of the fish where the enzyme is found, but generally, the tissue is homogenised and an isotonic buffer with an optimal pH is added. Then, the enzymesprecipitateto separate from the remaining tissues. After isolation, several enzymes need to be separated from each other. Depending on their composition and characteristics, the separation can be performed with different techniques such as size exclusion and/or ionic exchange chromatography or ultrafiltration [166, 167].The latest research on fish enzymes included the characterization of a digestive lipase from red sea bream [168], the identification and characterization of serpin8,which is a potential protease inhibitor [169], the molecular characterization of the gene that encodes cathepsin L [170], a new serine protease that interacts with an envelope protein of the white spot syndrome virus [171], chitin extraction using a digestive protease [172], molecular characterization and functional analysis of a salmon heme peroxidase [173] or the characterization of a lipase from liver of Sea bass [174].

Marine enzymes have a wide application in the food, chemical, pharmaceutical, cosmeceutical, agricultural and biotechnological industries [175]. Lipases catalyse the hydrolysis of ester bonds of several substrates, like triglycerides, phospholipids, and esters [176]. They have been employed in the production of renewable fuels to break the fatty acid chains into esters [177]and in the synthesis of structured lipids enriched by PUFAs, DHA or CLA, at a specific position [176]. Marine enzymes, namely proteolytic enzymes, are applied in molecular biology research field, for peptide synthesis, digestion of unwanted proteins during nucleic acid purification, cell culture and tissue dissociation, preparation of recombinant antibody fragments for research, diagnostics and therapy, peptide sequencing and proteolytic digestion of proteins in proteomics studies [178]. Proteases can alsohydrolyse peptide bonds. Acidic (pepsin) and basic proteases (trypsin, chymotrypsin, and elastase) can be found in fish viscera. They have several applications in food and pharmaceutical industries. For example, pepsin can be used in the collagen and gelatin extraction [65], and in the production of rennet that acidifies the milk to produce cheese [179]. Alkaline proteases from the viscera of three different species were used to deproteinize

shrimp wastes, and these can be applicable to the extraction and purification of chitin [160]. Trypsin isolated from the intestine of the carnivorous fish (*Mustelus mustelus*) showed high proteolytic activity under high NaCl concentrations (30%) establishing its potential to be employed in the hydrolysis reaction with high salt content [180].Another type of application for these enzymes is in the treatment of contaminated effluents and in peptide synthesis by the pharmaceutical industry. Van der Oost reviewed the capacity of some marine enzymes to be used as biomarkers of xenobiotic compounds, such as polycyclic aromatic hydrocarbons (PAHs), to detect environmental risk assessment. These enzymes are involved in the detoxification of these compounds and their metabolites due to their relatively low degree of substrate specificity .It was verified that the elimination of PAHs was very efficient and no bioaccumulation was observed in any fish organs or flesh [181]. Few studies have shown the effects of using enzymes isolated from fish in the treatment of marine wastes in a process called autolysis. Although it is a very economic procedure, it is difficult to standardize and control because endogenous enzymes depend on many factors, such as seasonality, fish species, amount and type of enzymes [182]. Bougatef produced protein hydrolysates from heads and viscera of sardinella (*Sardinella aurita*) using the fish enzymes present in the viscera. They found that the addition of an external enzyme can accelerate the reaction and increase the degree of hydrolysis [183]. Motamed zadegan investigated the proteolytic activity of the endogenous fish enzymes present in tuna by-products head, viscera and tails and added a neutrase produced by *Bacillus* sp. Two distinct fractions were obtained: one rich in peptides that size-wise ranged from medium to small and poor in lipids, and another with insoluble proteins and rich in lipids. This result also proves that the developed method can be an excellent method to separate the fish by-products in two fractions [184].Other studies have proved that fish hydrolysates obtained with fish wastes possess improved solubility in comparison with the raw substrate [185, 186]. Rodriguez et al mixed digestive proteases of Nile tilapia (*Oreochromis niloticus*) with other proteases obtained from the wastes of the following species: *Pleoticus muelleri*, *Artemesia longinaris*, and *Patagonotothen ramsayi*. This set of enzymes was intended to be used in a feed supplement to help the digestion efficiency of tilapia fingerlings and juveniles. The results showed that Nile tilapia proteases not only kept their activity in the presence of the exogenous enzymes, but its proteolytic activity was enhanced [187].Santos et al evaluated the capacity of combining fish enzymes, isolated from fish intestine, and fruit peels in the degradation of organic solid wastes. The results indicated that the weight loss and biodegradability percentage of these enzymes are comparable to the waste treated with a commercial enzymatic solution [188].

3. Lipids (fish oils)

Fish fatty acids are constituted by phospholipids, triacylglycerols (TAG), sterols (cholesterol) and minor quantities of unusual lipids, such as glycolipids and sulfolipids [189]. The TAG can be either saturated or unsaturated (mono or poly). Polyunsaturated fatty acids (PUFAs) possess a long chain with two or more double bonds [190]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are considered to be the most important fatty acids in fish. These fatty acids cannot be synthesised by humans so it becomes necessary to ingest them. Nevertheless, less frequently they can also result from a series of enzymatic reactions like chain elongation, desaturation, and β-oxidation of α-linolenic acid (ALA)occurring in the liver [191]. In the whole, fish fatty acids are located in the subcutaneous tissue, the belly flap, muscle tissue, liver, mesenteric tissue and head [192]. In fish wastes, fatty acids can be obtained mainly in the fish gut, head, and frame. In the obtained fish oils, PUFAs occur in the triglyceride form varying in concentration (between 10 to 25%) [190], and their amount is extremely variable depending on several factors such as water temperature, pH, salinity, reproductive cycle and feeding amounts [193, 194]. The extraction of fish oil from fish residues was initially performed by conventional extraction, fractionation, and purification methodologies. Processes such as hydraulic pressing [195], urea crystallization [196], solvent extraction [197, 198] and chemical hydrolysis [199] have been reported. Fish oil is a highly demanded product to several industries due to several health benefits that have been reported over the last decades for several pathologies, such as cardiovascular diseases [200], rheumatoid arthritis [201], psychotic disorders [202], metabolic syndrome [203], cancer [204] and bone fragility [205], among others. The traditional isolation methods present disadvantages due to the conditions applied, such as high temperatures [206] that degrade sensitive labile compounds, and the use of toxic solvents [207] that may leave residual solvent in the final products. These methods affect the fish oil quality and can even result in adverse

effects to the human health. The objective of all performed studies was the use of fish residues from processing industries to produce fish oils and other value-added compounds with the same quality, and if possible, the same composition of the actual fish oils obtained from whole fish. An important feature in this process is the condition of the starting raw material. The storage of the fish residues has to be performed to minimize possible microbial, chemical and enzymatic reactions. These processes may lead to increased oxidative breakdown that could affect the oil quality [208].

Thus, to overcome the adverse effects caused by traditional extraction methodologies, environmentally and extract friendly extraction techniques with high quality were employed on the extraction of fish oils, with a special highlight to enzymatic extraction and supercritical fluid extraction. The advantage of enzymatic extraction lies in low energy requirement, no solvent use and low investment for process industrialization [209]. Numerous research using this methodology to obtain fish oil from fish wastes have been performed. Mbatia et al investigated the use of commercially available enzymes to extract fish oil from the Nile perch and salmon heads, as well as, the effect of water on the obtained oil [210].Other studies reported the enzymatic extraction using commercial, low-cost food grade proteases under mild conditions to successfully extract oil also from Nile perch and salmon heads [211]. Vegneshwaran studied the use of enzymatic hydrolysis in different parts of cultured salmon wastes, namely gut, heads and frames. The author reported that the highest percentage yield was obtained in the guts. The obtained oil was rich in saturated fatty acids, monounsaturated fatty acids as well as polyunsaturated fatty acids with a high percentage in EPA and DHA revealing that the oil obtained from by-products has high value [212]. In another study, the authors compared the enzymatic extraction from the whole fish and compared to the oil obtained from the head, fin, tail, skin, and gut. The study concluded that the yields were higher in oils extracted from heads [213].

Another extraction technique applied for the recovery of fish oil from the fish residues is supercritical fluid extraction (SFE). To date, numerous studies have been carried out for the extraction of fish oil fatty acids using the SFE technique. This technique presents several advantages since the solvent used, CO_2 is non-toxic, non-flammable, inexpensive and clean. Additionally, the fish oils obtained using mild conditions (low pressures and temperatures) avoid compound degradation. In a study performed by Sarker, the optimized supercritical fluid extraction led to a 67.0% yield, which was higher than the Soxhlet procedure for the obtention of fish oil from the viscera of African Catfish [214]. Ferdosh examined the quality of the fish oils extracted using supercritical fluid extraction by processing the head, skin, and viscera of three neritic tuna species and compared to Soxhlet extraction. The yields were reported to be similar, and the oil content/yield among the studied species was negligible. Nevertheless, the composition of the different studied parts was significantly different. The total saturated fatty acids for all studied parts and the three different species were in a higher percentage than monounsaturated fatty acid (MUFA) or polyunsaturated fatty acid (PUFA) [215]. Fiori described the lipid profiles of trout head, spines, and viscera obtained by supercritical carbon dioxide and compared these results with a solvent extraction (Randall extraction with hexane). These authors account for a very high percentage of unsaturated fatty acids for all extracts. EPA and DHA content was also reported and significant differences were reported for the relative amounts of triacylglycerides (TAG), diacylglycerides (DAG) and free fatty acids (FFA) [216]. Rubio-Rodriguez studied four different fish by-products, specifically, offcuts from hake (*Merluccius capensis–Merluccius paradoxus*), orange roughy (*Hoplostethus atlanticus*) and salmon (*Salmo salar*), and livers from jumbo squid (*Dosidicus gigas*) with four different methods: cold extraction (CE) or centrifuging, wet reduction (WR), enzymatic extraction (EE) and supercritical fluid extraction (SFE). The comparison between the different studied extraction techniques showed that SFE could be useful in oil oxidation prevention. However, SFE co-extracted some endogenous compounds that increased the fish odour and acidity, which is known to reduce the oil quality. The possibility of fractionating the substrate is also feasible with the use of two separators and Rubio-Rodriguez has shown that the oil quality improved whilst the number of impurities reduced [217]. Ahmed performed supercritical and Soxhlet extraction of skins, scales, and bones of bigeye tuna. The authors reported, using mild conditions that SFE can yield a high-quality oil [218]. In another study, the SFE potentiality to reduce impurities was successfully studied with the extraction of toxic elements from fish oil, namely lead, cadmium, arsenic, and mercury [219].

4. Minerals (hydroxyapatite and calcium carbonate)

Hydroxyapatite is a mineral build of calcium phosphate, which is the primary inorganic constituent of bones and teeth in vertebrates [220]. Among several interesting biological properties hydroxyapatiteis non-toxic, non-inflammatory, non-immunity, biocompatible, bioactive and with high bioresorbability [221]. It is present in fish bones and scales as nanocrystals of approximately 5-20 nm width by 60 nm length with low crystallinity [222]. This marine mineral conserves its structure under physiological conditions, being thermodynamically stable at physiological pH and actively involved in bone reconstruction [5].

Several extraction methods to obtain hydroxyapatite have been reported. For fish scales usually, a thermal method is employed with temperatures ranging from 600 to 1400ºC.Piccirilloobserved that only hydroxyapatite was detected at 600ºC, between 1000 – 1200ºC β– hydroxyapatite was also detected, and when 1400ºC was used a dehydrated form of calcium phosphate was detected [16]. The hydroxyapatite extraction from fish bones can also be performed using other techniques, such as hydrothermal method [223], liquid membrane [224], precipitation [225], radio-frequency thermal plasma [226], ultrasonic precipitation [227], reverse microemulsion [228], sol–gel [229], polymer-assisted method [230], and subcritical water process [231]. When the hydrothermal method is applied, a pre-treatment of the bones is usually performed. The bones are washed with hot water to remove the meat, then soaked in an alkaline solution to remove any contaminants present. Then the substrate is subjected to a temperature of 900ºC to obtain the crystals [232].The preferred method used for bones and scales is thermal calcination since it is a relatively simple method that allows the formation of pure crystals. The crystals formed by this methodology have good crystallinity with dimensions between 0.3 – 1.0 μm [233, 234]. They are non-toxic and can be used in bone tissue engineering [235]. Recently the research on hydroxyapatite focused in the obtention of high purity material to be used in medical engineering [68, 236–239]. There are several potential applications for hydroxyapatite. Hydroxyapatite has the advantage to create composite biomaterials to construct scaffolds, with two or more distinct phases, combined with organic materials to be applied in tissue engineering [240]. The scaffold serves as physical support to allow the cells to migrate, proliferate and differentiate [241]. It is broadly used in the reconstruction of bone due to defects, injuries, or even cancer [242]. This inorganic material can also be used to fill teeth and in dental implants [243]. When combined with alginate it is used in porous scaffolds to reconstruct bones and cartilage [233].This inorganic compound can be used in nanoparticle drug delivery system since it does not interfere with the biological metabolism. Surface functionalization of hydroxyapatite nanocrystalsis able to selectively deliver drugs to treat bone cancer [244–247]. The advantage of using this nanocrystal as drug-carrier is the reduced toxicity of the therapeutic agent since it is not detected by the immune system and can also carry several drugs, such as antiviral agents [248] or DNA [249–251]. Hydroxyapatite doped with metal ionshas the capacity to absorb UV radiation. It presents photostability and does not cause skin irritation. It has an excellent absorbing capacity, even better than TiO_2 and ZnO that is usually used in sunscreens, with the potential to be incorporated in health and cosmetics products [252].

Enzymatic methods are an innovative method to extract hydroxyapatite that has the advantage of obtaining an excellent material that maintains its biological activity. This technique was performed *in vitro* using fish scales wastes, and the results confirmed that the mineral obtained through enzymatic hydrolysis has low crystallinity, nanoparticle sizes with a high Ca/P molar ratio and can promote the cell proliferation and differentiation of an osteogenic cell line [253]. It is a promising biomaterial to be used in medical materials being necessary to scale-up the process and perform *in vivo* controlled assays. Recently, it was demonstrated that hydroxyapatite can be successfully used in nanomaterials coating based on third-generation biomaterials with a wide application in medical devices. Shen studied the effect of coating a bilayer of hydroxyapatite using a microwave aqueous chemical route in magnesium alloys to be used as implants. The results showed that the coating increased the resistance of the implants proving that they are promising candidates for orthopedic applications [254]. Ai produced a hydroxyapatite nanowire coated with dopamine and silver particles to investigate their potential to be used in dental composite resins. The outcomes showed that this biomaterial possesses antibacterial activity and had no significant cytotoxicity [255]. Sun produced hydroxyapatite nanowire@magnesium silicate nanosheets (HANW@MS) to be used in orthopedics. The results showed that this nanomaterial released magnesium and silica simulating the formation of new bone enhancing *in vivo*its regeneration and blood vessels

[256]. Besin is tested the antibacterial potential of a titanium alloy implant followed with silver, titanium dioxide, and hydroxyapatite nanocoatings and verified it had successful antibiofilm property. These findings show that this biomaterial is a promising candidate to be used in dental implants [257].

5. **Complete valorization through other techniques**

The previously described processes that lead to a valorisation of the fish processing industry wastes by the extraction of bioactive molecules originate downstream wastes. These wastes can be further addressed as a substrate leading to minimal/zero waste with the consequent valorisation of the whole substrate. The whole use of the feedstock is already applied in other industries, like the cattle slaughter houses. Combined slaughterhouse waste obtained from the different processing areas are treated and processed originating several valuable by-products such as energy, methane, manure, animal feed, soap and candles [258]. This allows the processes to be sustainable and generate a greater economic value. Several options are presented here to treat the final fish residues. If the previous process yields a wet biomass, one option is to subject the residues to supercritical water gasification with the production of CH_4, H_2, CO, CO_2 and C1-C4 carbon gases. The formed side products, such as bio-oil, char and tar, can be used in the production of energy and mineral matter, and the latter can be used in agriculture [259]. Other options for fish residue valorisation were also reported, namely the production of lactic acid from the hydrolysis of fish meat and waste fish entrails [260, 261]and the use of minced residues to use as feed for fish or in agriculture fertilizer [262].

6. Conclusions

The generation of large amounts of organic waste and its disposal is resulting in adverse environmental, economic and social problems. Nowadays, there is a rising concern to create a society that has minimal wastes based on sustainable production and consumption practices. The use of converted bio-waste in manufacture processes or into final product formulations by several industries is increasing, as claims as "decrease greenhouse gas emissions" or "sustainable raw materials" are sought by consumers. In fact, the “Circular Economy” and the “zero waste goal” are considered as priorities and the only path for sustainable growth. In the case of Europe, the European Commission elected this topic as a primary focus for the next framework program [263].

The fish processing industry produces a high percentage of wastes that may range from 20 – 80% depending on several factors. These residues were thought to possess low economic value and contributed to the increase of environmental pollution. Nevertheless, research was able to determine that these wastes contain several active biological molecules. More recently, researchers are employing environmental friendly extraction techniques that are able to extract the value-added molecules and to maintain their biological function.

Several studies were performed and value-added compounds were successfully extracted from different fish residues. Collagen, enzymes, bioactive peptides, and gelatin were isolated from skin, scales, bones and muscles through enzymatic methodology. Polyunsaturated fatty acids (PUFAs) were obtained from fish residues using supercritical CO_2 extraction and pressing, whereas hydroxyapatite was obtained by calcination and enzymatic methods from fish bones, frames, and scales. These wastes will serve to produce value-added products to satisfy the needs of the market.

An exhaustive exploration of the fishery resources needs to be accomplished in a sustainable manner in the near future. The single use of a natural resource to satisfy the needs of a single industry is not feasible and the fish processing industry waste could be a benchmark to fulfil the highly desired minimal waste / high throughput industry. Thus, the concept of a marine biorefinery has to be applied for a sensible exploitation of the available marine resources. A biorefinery is a multiple process and multiple product system wherein the residue coming out of a treatment process is used as feedstock for another process, where a maximum treatment efficiency is achieved, thus supporting the circular economy concept. Therefore, and taking into consideration the goal of zero waste, a crucial objective is to fully use the whole fish residues leaving a zero carbon footprint instead of using some of the wastes to produce few distinct products such as fish oil, collagen or gelatin. To this extent, and to the best of our knowledge, no studies were performed to implement a methodology to use all the fish substrate and leave no residues, therefore leaving an open opportunity to fully accomplish a zero waste industry.

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