Review

Bioactive peptides from fisheries residues: A review of use of papain in proteolysis reactions

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ABSTRACT

Papain is a cysteine endopeptidase of vegetal origin (papaya (*Carica papaya* L.) with diverse applications in food technology. In this review we have focused our attention on its application in the production of bio-peptides by hydrolysis of proteins from fish residues. This way, a residual material, that can become a contaminant if dumped without control, is converted into highly interesting products. The main bioactivity of the produced peptides is their antioxidant activity, followed by their nutritional and functional activities, but peptides with many other bioactivities have been produced. Thera are also examples of production of hydrolysates with several bio-activities. The enzyme may be used alone, or in combination with other enzymes to increase the degree of hydrolysis.

1. Introduction

1.1. Biocatalysis, advantages, problems and solutions

Nowadays, the use of enzymes as industrial biocatalysts is experiencing a great development [1–5]. At first glance, enzymes are almost ideal biocatalyst due to their high activity under mild conditions, selectivity (that reduces the production of side-products) and specificity (that avoids the modification of molecules similar to the substrate). However, enzymes are biological catalysts, designed by natural evolution to fulfill their physiological function, e.g., enzymes must be able to give a response under stress situations [6]. That way, enzymes are relatively unstable, prone to inhibition by different compounds and the good features are manifested versus their natural substrates, while

industry wants to use enzymes with very different substrates.

In this context, the use of enzymes is benefitting from the development of very different tools to improve their features. Currently, researchers may utilize all present and former enzyme biodiversity thanks to metagenomics [7–9]. The selected enzyme features may be rapidly evolved in the industrial desired direction, thanks to directed evolution [10–13], and the new advances in enzyme immobilization [14–17] and chemical modification [18–20] open up new possibilities towards the implementation of enzymes in industry. These tools may be used in a combined way [21–25]. For example, nowadays it is possible to create an enzyme bearing two active centers (the so-called plurizymes) [26] and later on, to modify one of them with a specific irreversible inhibitor bearing an organometallic catalyst [27]. This way, the enzyme bearing two very different active centers may be used in a cascade reaction as a

unique catalyst.

The use of enzymes in food technology may have special relevance [28–31], as in many instances the production of by-products is critical, as it is not feasible to eliminate these side-products from the food. Similarly, enzyme specificity permits to modify just the target compounds, leaving the other food components unaltered, even very similar ones. In this context, proteases are one of the enzymes with a higher relevance [32–42].

1.2. Protease applications

Protease applications are broad and include the pharmaceutical and cosmetics industries, cleaning processes, sample preparation for analysis, and food and feed technological process [41–44]. Its applications in food processes are largely based on the effects achieved by modifications in proteins, natural substrates of proteases. Protein hydrolysis can alter its physical and chemical properties, leading to improvements in solubility, foaming capacity or emulsion, new sensory properties, reduced allergenicity, and improvements in nutritional properties, such as increased digestibility. These processes allow the development of new products and also the expansion of the use of protein sources that are not always used in human food, such as countless by-products and materials that could be discarded [41–44].

The range of applicable proteases is enormous, since proteases are present in practically all animal and vegetable tissues or microorganisms, because they have numerous physiological functions, they present an incredible variety of specificities and working conditions [43]. In other words, it is possible to choose the most adequate protease to be applied to a specific process considering the type of hydrolysis to be carried out (its specificity) or enzyme ability to withstand specific conditions of the medium, such as temperature, pH and the presence of components that could be inhibitors. Due to its great selectivity, with a well-planned choice, the product to be obtained is highly controllable, which is quite desirable in a process additive [41–44].

1.3. Bioactive peptides

One of the protease applications is a guided release of specific peptides [41,42]. Peptides, in addition to their nutritional characteristics as sources of amino acids, are known to also have beneficial health effects, as they can present the ability to interact directly with human metabolism routes, acting as health promoters and in the mitigation of aging process [45,46]. Recent research shows that peptides released from the diet can act directly on aging biomarkers, such as insulin resistance or mTOR pathway [47].

Peptides can act by different mechanisms, such as by inhibiting key enzymes in processes of metabolic disorders, such as angiotensin-converting enzyme inhibitors or DPPIV, or by unpaired electron captors, that is, acting as antioxidants. The different biofunctionalities are related to the characteristics of the peptides such as their composition and sequence of amino acids, type of amino acid present at the amino or carboxyl terminals and size. These characteristics provide greater or lesser solubility, hydrophobicity, among other characteristics that can directly interfere with its activity or even its potential to be absorbed and reach the action site [48]. Two important points of definition of these characteristics are the protein chain of origin of this peptide and the way in which this protein was "cut". The same hydrolyzed protein at different points in its chain will release different peptides and, probably, with different functions [34,40,41]. Based on this observation, research including different protein sources and different proteases as strategies for releasing these peptides has been successful in identifying a wide range of potential nutraceuticals. Fisheries residues proteins and the application of papain in their hydrolysis processes are examples of these successful endeavors.

1.4. Papain

Papain (EC 3.4.22.2) is an enzyme considered in the EC tree classification as "hydrolase" (EC 3.), which acts on peptide bond (EC 3.4.), and with the characteristic of being a "cysteine endopeptidase" (EC 3.4.22) [49]. This last categorization is more directly related to the substrate-enzyme interaction, since the action of endopeptidases includes the passage of the substrate through the region of the active site of the enzyme with the occurrence of cleavage in regions in the middle of the molecule. Its classification as "cysteine protease" refers to its mechanism of action, which brings the catalytic amino acid of its active site the cysteine-25, which together with Histidine-159 and Asparagine-175 constitute the catalytic triad of the papain protein chain [32,50]. In this context, papain preferentially cleaves peptide bonds involving basic amino acids, such as arginine or lysine, bearing a large hydrophobic side chain at the P2 position [49].

Commercial papain is generally obtained from papaya (*Carica papaya* L.), especially by cutting the skin of the unripe fruit to collect the latex, from which the enzyme is extracted, or simply dried this material to use the raw material. But papain-like proteases are found in many living organisms, such as plants, invertebrates or virus. Recently, the SARS-CoV-2-papain-like protease has gained prominence for its multiple functions evidenced for the coronavirus [51].

Papain derived from papaya is listed among the enzyme preparations recognized by the US Food and Drug Administration (FDA) as GRAS (generally recognized as safe) substance [52]. This, together with its wide pH range of action, (pH 3.0–9.0 depending on the substrate) [50], ensures a wide application of this enzyme in food processes. In this way, it can be considered a "food additive" and used as a process additive in food preparation, gaining more and more applications, being used in processes such as meat tenderization, thanks to its hydrolysis action of myofibrillar proteins or in baking and milk industry, acting in the alteration of food flavor and reduction of allergenicity [32]. In addition, its protein hydrolysis processes have demonstrated a high potential for the release of bioactive peptides from different sources.

1.5. Use of industrial food wastes: fishing factories residues

The production of wastes from food industries is necessary, including these materials in a circular economy, as these wastes are affecting to land, energy, water and labor, and generating environmental problems [53–58]. That way, the development of strategies for the use of these wastes is indeed a necessity [59,60]. The implementation of circular bioeconomy models has become a priority [61–65].

Food wastes have been used as feedstock to produce valuable products [66–70]. or to produce bioethanol [71], biolubricants [72] while bioplastics have been produced from various biomass sources [73]. In this context, the production of bioactive compounds has a special interest [74–78], This is the main topic of the current review, the production of bioactive peptides using residues from the fishing factories.

Fishing production (extractive and aquaculture) reached a volume of 210.9 million tons in 2018 [79] generating. large amounts of fishery waste and by-products every year. It has been reported that 60% of the processed fish are discarded (muscle (15–20%), viscera (12– 18%), bones (9–15%), heads (9–12%), scales (5%) and skin and fins (1–3%)) [80–84]. These fish wastes are an excellent source of protein (skin), calcium (trimmings and bones) and lipids (head, intestines, and bones). On a dry basis, the chemical composition of all fish byproducts is 49.22–57.92% for protein content, 21.79–30.16% for ash content and 7.16–19.10% for fat content [85–87]. These residues are usually either underutilized to produce low market value products or dumped in Nature, leading to environmental issues [88]. In this sense, it is imperative to implement bioeconomic models that allow the integral use of fishing biomass to obtain added value products (such as peptides, chitin, collagen, enzymes, polyunsaturated fatty acids and minerals) and low environmental impacts [89,90].

Waste from the fishing industry has been utilized to produce flour and fertilizers, and for obtaining oils, biopolymers (chitin and chitosan [91,92]. Diverse enzymes have been obtained from these residues (e.g., pepsin,). orlipases [93–95]). Scales from *Lutjanus* sp. and *Anabas testudineus* have been used for obtaining chitin and chitosan [96,97], both of them, very attractive compounds for using in fields such as cosmetics and food industries, medical, nutraceuticals, pharmaceutical, gene therapy and bioremediation [98]. On the other hand, fertilizers made from fish waste have been successfully used in the horticultural industry, improving the quality of plants and soils after their application [99]. The biofuel production from fish waste is also a common objective [100]. The use of fish residues for the production of flour has also proven to be a sustainable alternative, even when the flour is used to enrich commercial flours such as wheat [101–102].

It should be interesting to change the way these wastes are used towards a biorefinery approach, which will allow the integral and sustainable use of the residual biomass from the fishing industry and transform it into highly marketable bio-based products [103]. In this context, the proteins present in fishing residues may become relevant beyond their nutritional value, since a set of peptides may be released when they are hydrolyzed employing proteases like papain, pepsin, trypsin, Alcalase, etc. The peptides obtained after this process are characterized by present biological and technological properties such as, antioxidant activity, anti-inflammatory capacity, antimicrobial capacity, capacity to inhibit angiotensin converting enzyme (ACE) [104–107], foaming capacity, emulsifying capacity and water and oil retention capacity [108] properties, which are of great interest and widely used as functional ingredients, nutritional supplements, and flavor enhancers in food, beverage and pharmaceutical industries [88,109,110]. They are the so-called bio-functional peptides, the target of this review.

2. Production of bioactive peptides by papain hydrolysis of proteins from fish residues

Fishery industry generates large quantities of fish by-products (heads, viscera, trimmings, roes, frames, cut-offs, skin, and bones) which contain important nutrients, mainly protein and lipids, which can be used to process them into added-value products. Particularly, these wastes contain a high amount of protein-rich material with a crude protein content of 8 to 35%, that are usually converted into low market-value products, such as fish meal, animal feed and fertilizer [111–113]. Different types of proteins can be found in fish residues. For example, in skeletal muscles there are three large groups of proteins, myofibrillar, stromal and sarcoplasmic proteins [114,115], among which proteins such as myosin, actin, actinin, α-actinin, calpains, cathepsins, albumin, creatine kinase, aldolase and collagen stand out among others [116–118]. This diversity of proteins makes the residues of the fishing industry ideal raw material for the production of bioactive hydrolysates, which have good amino acid profile and nutritional composition, and are considered the largest source of bioactive peptides, which are of great relevance for industries such as food and pharmaceuticals, among others. Production of bioactive peptides from fish residues led to take better advantage of protein-rich wastes, as well as to reduce environmental pollution caused by improper disposal of these wastes [111,119–123].

Bioactive peptides are protein fragments that upon release from the parent protein through an appropriate method, express one or more biological or functional activities [124,125]. The bioactive properties of peptides can be exploited in two ways, either as hydrolysates, that is, as a mixture mainly composed of amino acids and peptides, or as bioactive purified peptides [126]. According to their degree of hydrolysis and main application, protein hydrolysates have been classified into three groups, namely, hydrolysates with a low degree of hydrolysis which have improved functional features, hydrolysates with various degrees of hydrolysis mainly used as flavorings, and hydrolysates with high degree of hydrolysis, which are commonly used in special medical diets and as

nutritional supplement [127]. On the other hand, most of the bioactive peptides are characterized by having molecular masses lower than 6000 Da and a size of between 2 and 20 amino acids [124,128,129]; these bioactive peptides have been widely related to many biological activities such as immunomodulatory, antimicrobial, antithrombotic, antioxidative, hypocholesterolemic, antihypertensive, and others. It is important to highlight that such bioactivities are determined by the structural properties of the peptide, as well as by its size and the amino acid composition, the later determined in turn by the specificity of the protease and degree of hydrolysis of the parent protein [124,130–133].

Hydrolysates and peptides can be obtained from food proteins by chemical treatment, solvent extraction, microbial fermentation and enzymatic hydrolysis using proteases [126,134]. Enzymatic hydrolysis is a process that takes place under controlled mild conditions, has high specificity, and unlike other methods, it does not leave toxic chemical residues or residual organic solvents in the obtained product; for this reason, it is the preferred method for obtaining bioactive peptides, especially for industries such as food and pharmacological [135,136]. In fact, due to these advantages, the enzymatic method is widely used to improve functional and nutritional properties of proteins [137,138].

Different protease enzymes such as Flavourzyme, Alcalase, pepsin, Neutrase, trypsin, Protamex, Corolase, chymotrypsin and papain, have been used for the production of protein hydrolysates [34,139–142]. In 1982 papain was successfully used to prepare hydrolysates from fish proteins [143], and since then, this enzyme has continued to be of interest in recent research. In this way, papain was used to improve protein recovery from different protein-rich industrial by-products, among them salmon viscera [144]. Hariyati et al., found that papain enzyme was excellent in producing snakehead fish (*Channa striata*) protein hydrolysate [145]; and Ren et al., showed that the optimum enzyme to hydrolyze bonito fish protein was papain [146]. However, it is important to mention that, one of the most important factors for the production of bioactive peptides is specificity of the enzyme used for the hydrolysis; that is to say, the use of different proteases to hydrolyze some protein substrate, will produce a variety of hydrolysates with different activities [136,147,148]. In addition, operation conditions of enzymatic hydrolysis such as time, pH and temperature (according to the enzyme features), and enzyme to substrate ratio, are factors that have an important influence on the degree of hydrolysis of the protein substrate, and as previously mentioned, the degree of hydrolysis has a great influence on the amino acid composition and size of the peptides, which could determine their biological and functional activity [149]. In this sense, several authors focus on the operating conditions, the degree of hydrolysis and the characteristics of the hydrolysates or peptides obtained, generally evaluating more than one enzyme. For instance, different degrees of hydrolysis were obtained when Alcalase and papain were used to hydrolyze fish protein from freshwater catfish (*Clarias batrachus*) [150]. On the other hand, protein hydrolysates were prepared from Bombay duck (*Harpodon nehereus*) by the combination of commercially available papain and Flavourzyme. Other authors studied the influences of hydrolysis time and enzymes substrate ratio on the degree of hydrolysis. It was found that at optimal hydrolysis conditions a degree of hydrolysis of up to 19.7% was obtained, and the molecular mass of hydrolysates was between 219 and 5245 Da [151]. Other study deals with the optimization of the hydrolysis conditions for the production of fish collagen peptides from skin of Malabar grouper (*Epinephelus malabaricus*) using pepsin, papain and protease from bovine pancreas. The optimum response of degree of hydrolysis was estimated to be 10, 20 and 28% for pepsin, papain and protease, respectively, and the electrophoretic pattern indicated that the molecular weights of the peptides formed by the hydrolysis were nearly 2 kDa [152]. In another paper, it showed that the use of trypsin, Corolase PP and a mixture of papain and bromelain to hydrolyze salmon backbone gave the highest yield of fish protein hydrolysates, while use of Protamex and Corolase PP resulted in fish protein hydrolysates with the best sensory properties leading to the lowest bitterness [153]. Noman et al. showed that

enzymatic hydrolysis conditions, especially enzyme type, affects the structural and physicochemical characteristics of protein hydrolysates prepared from Chinese sturgeon through the enzymatic hydrolysis with papain and Alcalase 2.4 L. They found that papain enzyme significantly increased the degree of hydrolysis (20.62%) and decreased the ζ-potential (12.4 ± 1.31 mV), while Alcalase 2.4 L hydrolysate exhibited smaller particle size (822.047 ± 61.26 nm) than papain hydrolysate (1425.39 ± 44.82 nm). In addition, hydrolysis by papain and Alcalase 2.4 L enzymes decreased the molecular weights (MW ≤ 1000 Da) to 98.27% and 86.84%, respectively [154].

Due to the foregoing, the process of hydrolysis of fish waste proteins through the application of proteases such as papain, becomes a sustainable method with good results to achieve a high recovery of proteins in the form of bioactive peptides from fishing industry waste. In this sense and with the aim of highlighting the value of the hydrolyzed fish residues obtained using papain, a relationship of the biological (antioxidant, angiotensin I–converting enzyme inhibitory activity, antimicrobial activity, binding activity, surfactant activity, anti-obesity activity, anti-anemia activity, anticholesterolemic activity and platelet activating factor acetylhydrolase (PAF-AH) inhibitory), nutritional and technological properties (water and oil absorption, gelling capacity, solubility, viscosity, foam and film formation and, emulsifying capacity) evaluated in different scientific studies is presented.

2.1. Production of peptides with antioxidant activity

2.1.1. Interest of the antioxidant peptides

Free radicals are generated by metabolic processes and chemical reactions [155], and its uncontrolled production and presence is related to a series of negative effects both on human health and food quality. When the levels of these highly reactive species are out of balance, they can cause damage in proteins, oxidation of membrane phospholipids, modification of low density lipoproteins (LDL) and even mutations in DNA, which can induce many health disorders such as cancer, atherosclerosis, diabetes mellitus, neurodegenerative and inflammatory diseases [126,156–159]. On the other hand, it has been reported that the oxidation of lipids and formation of secondary lipid peroxidation products during processing and storage of food, affects the food quality by alterations of several organoleptic properties like color, texture and flavor, and even the loss of nutritive value [132,136].

In order to prevent deterioration in food quality, various synthetic antioxidants such as propyl gallate, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have been used [126,159]. Nevertheless, despite the potent antioxidant activity of these chemical compounds their use has been restricted, because they present some toxic effects and can induce DNA damage [126,159]. For this reason, nowadays there is a growing interest in finding new, healthy and innocuous natural compounds with antioxidant activity, which can be used in the promotion of healthcare, as well as in food preservation [136,160].

Compounds such as carotenoids, phenolic acids, flavonoids, vitamin E and C and α-tocopherol, which are found naturally in seeds, fruits and vegetables, possess these antioxidant activities [136,161–163]. In addition, it has been reported that protein hydrolysates and peptides produced by enzymatic hydrolysis of proteins may present various biological activities, among which, antioxidant activity has been the most studied, finding that such antioxidant peptides (usually small peptides) are healthy and safe compounds and possess high activity and easy absorption with low cost [34,126,164]. In this sense, the production of antioxidant peptides from fishery resources has been widely investigated, as they are easy to obtain, cheaper in cost, and do not have side effects, for their use on health, pharmaceutical and food industries, as an alternative to make efficient use of the fishing industry resources, minimizing waste generation by obtaining bioactive compounds with added value [34,88,165–168].

It is well known that enzymatic hydrolysis is an effective method for the preparation of bioactive peptides, thus, for the production of antioxidant peptides, many enzymes like Alcalase, Protamex®, Flavourzyme®, chymotrypsin, trypsin, pepsin, and papain have been widely used [136,169,170]. In the context of the current review, examples of the use of papain in the production of peptides and hydrolysates with antioxidant activity obtained from fish waste proteins, are presented below.

2.1.2. Production of antioxidant peptides using papain

In an interesting research effort, papain and other proteases (pepsin, trypsin, α-chymotrypsin, Alcalase and Neutrase) were employed to produce antioxidant hydrolysates from hoki frame protein, and after 7 days of lipid autoxidative reaction, papain hydrolysates prevented 45% of lipid peroxidation in the linoleic acid emulsion system [171].

Residues of various species of tuna are a popular substrate to this goal. For example, Je et al., reported the hydrolysis of tuna backbone protein using six different proteases, including papain. Lipid peroxidation inhibition assay in linoleic acid emulsion model system showed that the hydrolysates could act as significant retarders of lipid peroxidation [172]. In another work, papain, Alcalase, α-chymotrypsin, Neutrase, pepsin, and trypsin were used to hydrolyze bigeye tuna (*Thunnus obesus*) dark muscle and all hydrolysates showed free radical scavenging activities against α,α-diphenyl-β-picrylhydrazyl (DPPH), hydroxyl, superoxide and alkyl radicals in an enzyme dependent manner [173]. In another research effort, tuna (*Euthynnus affinis*) red meat proteins were hydrolyzed using papain (0.5% *w*/w). After 45 min of hydrolysis, the produced hydrolysate exhibited a DPPH scavenging activity and a reducing power of 56.82 ± 0.74% for 2 mg/mL protein and 0.614 ± 0.009 for 10 mg/mL protein, respectively. Results showed that dip treatment in 0.5% hydrolysate solution significantly reduced (p < 0.05) the oxidation of ice stored dressed sardine [90]. In addition, scale gelatin from skipjack tuna (*Katsuwonus pelamis*) were prepared and separately hydrolyzed by five proteases (pepsin, papain, trypsin, Neutrase, and Alcalase). Papain hydrolysate exhibited a hydroxide radical (HO·) scavenging activity of 16.58 ± 0.93% [174].

Retorted cobia (*Rachycentron canadum*) skin gelatin hydrolysate was treated using bromelain, papain, pancreatin and trypsin digestion. The maximal DPPH radical scavenging effects of 10 mg/mL of the papain hydrolysate was 57.6% (after 2 h of reaction), with a lipid peroxidation inhibition (10 mg/mL) of 60-71% on the fifth day using a linoleic acid model system [175]. Another interesting investigation reported the use of enzyme-assisted oil aqueous extraction using commercial proteases such as Alcalase, papain, trypsin, and pepsin to simultaneously increase oil extractability and recovery of protein hydrolysates from cobia (*Rachycentron canadum*) liver. The cobia liver hydrolysates obtained from enzyme-assisted aqueous extraction by papain pretreatment showed scavenging DPPH radical activity with EC50 values of 1.03 mg, and after in vitro simulated gastrointestinal digestion, the EC50 value for scavenge DPPH radical activity remained similar 1.55 mg [176].

Several investigations have focused on the use of different carp residues for their conversion into hydrolysates with antioxidant activity. For example, myofibrillar protein from grass carp was hydrolyzed using papain, pancreatin 6.0, bromelain, Neutrase 1.5MG, and Alcalase 2.4 L, and the hydroxyl radical scavenging activity of the papain hydrolysate presented an IC50 of 701.18 ± 17.63 μg/mL [177]. In another research, grass carp protein hydrolysates were prepared using Alcalase 2.4 L or papain. It was found that, as the degree of hydrolysis increased, the reducing power and DPPH• scavenging activity decreased for both hydrolysates [178]. Hydrolysates of papain at the same degree of hydrolysis possessed higher radical DPPH scavenging activity (77.63 ± 0.98%) and reducing power (0.55 ± 0.01) than Alcalase hydrolysates [178]. Another study reported that papain-treated grass carp protein hydrolysate could chelate 50% of Fe^{2+} and scavenge 50% of hydroxyl radicals at a concentration of 0.81 and 8.12 mg/mL, respectively [179]. In addition, papain hydrolysate could decrease peroxide values and inhibit the formation of thiobarbituric acid reactive substances in fish mince throughout storage, at the application level range from 0.5% to

4.0% [179]. Another example shows that the hydrolysates obtained from the scales of silver carp (*Hypophthalmichthys molitrix*) by papain for 10 min, Flavourzyme for 5 min or Alcalase 2.4 L for 5 min exhibited important in vitro antioxidant activities in silver carp mince and surimi gels during storage at 4 °C [180]. In another paper, an antioxidant grass carp protein hydrolysate was prepared by papain hydrolysis. The hydrolysate showed a stable metal chelating activity and reducing power in a temperature range from 40 °C to 100 °C and in a pH range from 3 to 9, and could still scavenge 63.8% of DPPH radical and chelate 70.5% ferrous ions in the presence of glucose, sucrose or NaCl [181]. Finally, fins from silver carp (*Hypophthalmichthys molitrix*) were hydrolyzed by employing four enzymes (trypsin, Alcalase, papain or Neutrase) [182]. The antioxidant activity of the papain hydrolysate exhibited an in vitro scavenging activity against 2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals of approximately 50% [182].

It was reported that peptides from loach (*Misgurnus anguillicaudatus*) prepared by papain digestion could scavenge DPPH (IC50 17.0 ± 0.54 mg/mL) and hydroxyl radicals (IC50 2.64 ± 0.29 mg/mL), inhibiting the lipid peroxidation in a linoleic acid emulsion system and chelate cupric ion [183]. Moreover, they can increase the activities of glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase (CAT) [183]. In another research, loach protein hydrolysates prepared by papain digestion were fractionated into four fractions and evaluated in terms of their in vitro antioxidant and antiproliferative (anticancer) activities [184]. The fraction IV exhibited stronger antiproliferative activity for human liver (HepG2), breast (MCF-7), and colon (Caco-2) cancer cell lines in a dose-dependent manner and showed the highest oxygen radical scavenging capacity (ORAC) value (215 ± 5.9 mM Trolox/100 g loach peptide when the concentration was 60 μg/mL) and the lowest IC 50 value (16.9 ± 0.21 mg/mL) for hydroxyl radical scavenging activity [184].

Several enzymes (Alcalase, trypsin, pepsin, Neutrase, α-chymotrypsin and papain) were evaluated to obtain antioxidant peptides from Pacific cod (*Gadus macrocephalus*) skin gelatin; being the papain hydrolysate the one that exhibited the highest antioxidant activity [185]. After peptide purification, two potent antioxidant peptides with amino acid sequences Thr-Cys-Ser-Pro (388. Da) and Thr-Gly-Gly-Gly-Asn-Val (485.5 Da) were obtained. They could be used as functional ingredients in the food industry with potent antioxidant benefits [185].

Antioxidant protein hydrolysate from giant kingfish *Caranx ignobilis* ([169], muscle and skin were obtained employing papain, pepsin, trypsin and α-chymotrypsin. Antioxidant activities of the papain hydrolysates (5 mg/mL) were $20.3 \pm 1.5\%$ and $19 \pm 1.0\%$, using DPPH radical scavenging activity for fish protein hydrolysate of muscle and skin, respectively [169]. In another research, muscle of seer fish (*Scomberomorus commerson*) was hydrolyzed using pepsin, trypsin and papain, finding that the three hydrolysates exhibit important antioxidant activities [186].

In another work, properase E, pepsin, trypsin, Flavourzyme, Neutrase, gc106 and papain were used to hydrolyze Tilapia frame protein to produce antioxidant peptides. In this case, papain hydrolysates showed antioxidant activities on scavenging DPPH radical, superoxide anion radical ($\cdot O_2$), hydrogen peroxides (H_2O_2) and hydroxyl radical ($\cdot OH$) of $41.5 \pm 2.1\%$, $26.1 \pm 1.6\%$, $50.7 \pm 2.8\%$ and $59.6 \pm 1.6\%$, respectively [187]. Later, gelatin hydrolysates from Nile tilapia skin were produced by hydrolysis with proteases, including papain, bromelain, trypsin, Favourzyme, Alcalase or Neutrase [188]. It was found that low molecular weight gelatin hydrolysate peptides (<10 kDa) had a great potential as antioxidant agents. Papain hydrolysate exhibited an activity on ABTS radical scavenging of 256.02 ± 121.86 μg trolox/mg protein and inhibits the oxidation of linoleic acid at a $41.56 \pm 1.22\%$ [188].

Hydrolysates prepared from the skin protein of seela fish (*Sphyraena barracuda*) and ribbon fish (*Lepturacanthus savala*) through enzymatic hydrolysis using pepsin, trypsin, and papain showed high antioxidant activity. Particularly, papain hydrolysates of the skin of both seela and ribbon fishes showed DPPH scavenging activities of 51.9 ± 4.1 and 45.0

$\pm 3.4\%$ (p < 0.05), respectively [189]. In a further research, papain, pepsin, trypsin, Neutrase, Alcalase, kojizyme, Protamex or α-chymotrypsin were used to produce hydrolysates from flounder fish (*Paralichthys olivaceus*) [190]. The antioxidant activities of papain hydrolysate measured as IC50 values on DPPH, hydroxyl and peroxyl radicals were 5.850, 0.666 and 0.244 mg/mL, respectively.

Anchovy sprat (*Clupeonella engrauliformis*) hydrolysates with high antioxidant activities were obtained by hydrolysis using proteases. Antioxidant activity determined by ferrous chelation, reducing power and DPPH assays was the highest in papain, bromelain and Promod® hydrolysates, respectively [191]. In another research effort, papain and pepsin digestion was used to hydrolyze backbones of Indian mackerel (*Rastrelliger kanagurta*) [88]. The obtained hydrolysates are potent antioxidants and exhibited significant reducing power and lipid peroxidation inhibition. Papain hydrolysate showed a scavenging capacity of 36% and 37.54% for DPPH and superoxide radicals, respectively [88]. Later, papain, Alcalase, neutral protease, trypsin or pepsin were evaluated to hydrolyze muscle protein from round scad (*Decapterus maruadsi*) [160]. Papain hydrolysate showed an antioxidant activity determined as scavenging activity of DPPH, superoxide radical and reducing power of 40.21 ± 0.85, 20.78 ± 1.44 and $0.260 \pm 0.018\%$, respectively.

Collagen obtained from different fish is a recurring raw material in the preparation of peptides/hydrolysates. For example, collagen peptides from fish and bone of Striped Catfish (*Pangasius pangasius*) possessing antioxidant activities were prepared by papain hydrolysis [192]. Collagen peptides from fish skin and fish bone exhibited the highest antioxidant activity after 160 min of incubation, with a DPPH radical scavenging activity of 71.55% and 63.06%, respectively [192]. In another study, collagen hydrolysates of redlip croaker (*Pseudosciaena polyactis*) scales were prepared using six different proteases (Flavoenzyme, pepsin, papain, trypsin, Neutrase, or Alcalase), and the hydrolysate prepared using papain with a degree of hydrolysis of $16.95 \pm 0.76\%$ showed a DPPH· radical scavenging activity of $26.33 \pm 1.37\%$ [193].

Moreover, protein hydrolysates were prepared from *Liza klunzingeri* muscle by enzymatic hydrolysis with papain at enzyme/substrate ratios of 1:25 and 1:50 for 45, 90 and 180 min, and their antioxidant and cytotoxic properties were evaluated [194]. Hydrolysates exhibited good scavenging activity on DPPH (IC50 = 3.18-2.08 mg/mL), ABTS (IC50 = 0.60-0.12 mg/mL) and hydroxyl (IC50 = 4.13-2.07 mg/mL) radicals, and cytotoxic activities against the 4 T1 cells (IC50 = 1.62-2.61 mg/mL) [194]. In another attempt, the same raw material was hydrolyzed with papain to obtain *Liza klunzingeri* protein hydrolysate rich in low molecular weight peptides (<1000 Da) with strong scavenging activity on ABTS (IC50 = 0.12 ± 0.016 mg/mL), DPPH (IC50 = 2.08 ± 0.13 mg/mL) and hydroxyl (IC50 = 2.07 ± 0.31 mg/mL) radicals [195]. In addition, *L. klunzingeri* protein hydrolysate at doses of 300 and 600 mg/kg significantly decreased lipid peroxidation and improved total antioxidant capacity in serum, liver, and kidney of the CCl4 exposed rats [195].

Different hydrolysates with varying antioxidant capacities were prepared using either papain or Alcalase at 1%–3% (w/w protein) for 0–240 min from two forms of salmon frames named "chunk" and "mince" [196]. Also, salmon bones were hydrolyzed by using one of four proteases (Alcalase, Favourzyme, Neutrase or papain) at various concentrations, finding that the hydrolysate derived from 10 mg/mL papain hydrolysis exhibited the highest nitric oxide (NO) radical scavenging activity [197].

In another research effort, antioxidant spray dried protein hydrolysate from *Pangasius* viscera by enzymatic (papain and pepsin) or chemical methods (hydrochloric acid and sodium hydroxide) were prepared [106]. Among the different treatments, DPPH free-radical scavenging activity of papain-extracted hydrolysate was $43.15 \pm 2.99\%$ at 0.4 mg/mL [106]. Later on, papain was evaluated in the production of antioxidant hydrolysate from Pacific herring (*Clupea pallasii*) protein; however, among the other assayed enzymes (pepsin, trypsin,

Flavourzyme, and Neutrase) papain hydrolysate showed the lowest cellular antioxidant activity [198].

Other studies deal with the optimization of hydrolysis conditions to obtain maximum degrees of hydrolysis or higher antioxidant activity. In this sense, antioxidant peptides from fish skin gelatin were obtained by papain hydrolysis after optimization of the reaction conditions[199]. The highest degree of hydrolysis ($50.1 \pm 1.1\%$) was obtained using an enzyme to substrate ratio of 2% at 56.8 °C and 2.11 h, while the highest DPPH ($96.8 \pm 0.9\%$) and ABTS (9.80 ± 0.11 mM Trolox [6-hydroxy-2,5,7,8-tetramethychroman-2-carboxylic acid]) radical-scavenging activities were obtained at an enzyme to substrate ratio of 3% at 52.1 °C after 2.65 h of hydrolysis [199]. Tuna meat protein previously treated under 500 W microwave at 50 °C for 10 min was converted into a hydrolysate after optimizing the reaction conditions (45 °C, 6 h, Trypsin 15000u/g, Papain 45000u/g and pH 7) to reach a degree of hydrolysis of 15.83%. The hydrolysate was fractioned by ultrafiltration obtaining three fractions (less than 5000 Da, 5000 ~ 10,000 Da, more than 10,000 Da) with a DPPH radical scavenging power of 9.08%, 9.55% and 9.30%, respectively [200]. In another paper, papain hydrolysate prepared from sea urchin (*Strongylocentrotus nudus*) gonad showed to be effective in the scavenging of hydrogen peroxide (EC 50 = 16.40 ± 0.37 mg/mL) and hydroxyl radical (EC 50 = 13.29 ± 0.33 mg/mL), inhibit lipid peroxidation (EC 50 = 11.05 ± 0.62 mg/mL), chelate Fe^{2+} (EC 50 = 7.26 ± 0.44 mg/mL), and protect mice macrophages against death induced by tert-butyl hydroperoxide, at the maximum degree of hydrolysis ($27.96 \pm 0.54\%$) obtained after reaction optimization (48.83 °C, pH of 6.92, enzyme-to-substrate ratio of 3143 U g^{-1}, and substrate concentration of 83.5 g/L) [201]. Antioxidant activities of ethanolic and methanolic tissue extracts from stone fish (*Actinopyga lecanora*) were improved by enzymatic proteolysis using different proteases [202]. Papain-generated hydrolysate exhibited the highest increase in antioxidant activity up to 85%, followed by Alcalase (77%), trypsin (75%), pepsin (68%), bromelain (68%), and Flavourzyme (50%) measured by DPPH• radical scavenging activity [202]. Also, papain hydrolysis of protein from small yellow croaker (*Pseudosciaena polyactis*) was optimized (60 °C, 4 h, enzyme concentration of 0.2% and meal/water ratio of 1:5) to give the highest degree of hydrolysis (49.50%) [203]. This hydrolysate possessed the highest antioxidant activity (IC50 value of 2.93 ± 0.027 and 9.16 ± 0.062 mg/mL for DPPH and hydroxyl radicals, respectively) [203]. In another paper, papain hydrolysis of fish-scale gelatin was optimized to obtain antioxidant hydrolysate [204]. The hydrolysate produced under optimal conditions (3% enzyme-to-substrate ratio, 55 °C, and 3 h had a degree of hydrolysis of 73.3 ± 0.5) a DPPH radical scavenging activity of $64.1 \pm 0.9\%$, an ABTS radical scavenging activity of 480 ± 1 mM Trolox/g, and a FRAP value of 9.1 ± 0.1 mM $Fe_2SO_4.7H_2O$/g [204].

2.1.3. Combined use of papain and other proteases

The combined use of several proteases is a common strategy to get a higher degree of hydrolysis [34,40], as it permits to combine different enzyme specificities [205]. That way, the use of papain in sequential hydrolysis system coupled to other proteases has also been reported.

For example, the production of gelatin hydrolysate from skin of unicorn leatherjacket was carried out by autolysis-assisted process mediated by indigenous protease from unicorn leatherjacket in combination with hydrolysis using papain [206]. It was found that prior autolysis could enhance the yield and antioxidant activity of gelatin hydrolysates, when subsequent hydrolysis by 2% papain was implemented. Hydrolysates showed metal chelating activity as well as ABTS radical and H_2O_2 scavenging activities [206].

In another paper, papain and an alkaline protease were used together to *co*-hydrolyze collagen polypeptide extracted from cod skin. It was found that under optimal hydrolysis conditions (using an alkali protease and papain content of 4 and 4.5%, respectively, 55 °C, pH 8 and 11 h), hydrolysates with good antioxidant activity were produced [207]. In another study, proteins of hairtail (*Trichiurus japonicas*) muscle were separately hydrolyzed using five enzymes, finding that the hydrolysates

of papain- and Alcalase- showed higher antioxidant activities than those produced by the other three protease (trypsin, Neutrase and pepsin) hydrolysates [208]. In a next step, papain plus Alcalase were jointly used in a binary-enzymes hydrolysis process to produce hydrolysate from hairtail muscle. After purification by ultrafiltration and chromatography technology, eight antioxidant peptides were purified, among them, TJP3, TJP4, and TJP8 exhibited strong scavenging activities on DPPH• (EC50 0.902, 0.626, and 0.663 mg/mL, respectively), HO• (EC50 1.740, 2.378, and 2.498 mg/mL, respectively), superoxide anion radical (EC50 2.082, 2.538, and 1.355 mg/mL, respectively), and ABTS radical (EC50 1.652, 0.831, and 0.586 mg/mL, respectively) [208].

2.2. Production of peptides with nutritional and functional activities

Fish represents a product of great value for the food industry not only because of the nutritional composition of the edible parts, but also because the residual tissues of the fishing industry (skins, bones, viscera, heads, fins, etc.) possess proteins with surfactant (foam and film formation and emulsifying capacity) and hydrodynamic (water and oil absorption, gelling capacity, solubility and viscosity) technological characteristics [108], which confer great potential to residues for their use in the development of new food systems. Despite these characteristics, the use of proteins in their native form directly in food systems has been limited because most foods have pH values close to the isoelectric point of proteins favoring its precipitation. This problem can be solved hydrolyzing proteins employing proteases, a process that allows to take advantage of the functional properties of proteins in a varied spectrum of pH [209]. The hydrolysis of proteins not only allows them to be used at different pH values but also peptide fractions of different molecular weights and with different properties can be obtained, expanding the range of uses within the food industry, if the appropriate proteases are used.

In a search carried out in Scopus, different articles were found related to the production of peptides with functional properties from fish using papain as a hydrolyzing agent. Although the oldest publication obtained with the search criteria dated from the year 1976, it was not until three years later that an article mentioned the hydrolysis of fish proteins using papain. This work was carried out by Beddows and Ardeshir, (1979), who obtained higher volumes of hydrolysates from insoluble fish proteins and using papain to hydrolyze, it than those traditionally obtained in the elaboration of fish sauce [210]. Years later, it was reported that the hydrolysis of eggs of *Cirrhinus mrigala* with papain, resulted in a hydrolysate with potential for use in the food industry due to its fat absorption capacity (1.0 g/g sample), foaming capacity (25%) and emulsifying capacity (5.98 ml/g of hydrolysate) [211]. In this sense, the use of papain in the elaboration of a protein hydrolysate from the muscles of the Chinese sturgeon (*Acipenser sinensis*) resulted in a product with a 79.67% protein content, a solubility greater than 86%, emulsifying capacity between 11.0 and 13.27 m^2/g with a stability index greater than 94%. Additionally, the hydrolysate presented a water retention capacity of 1.93 g H_2O/g of protein, an oil retention capacity of 2.59 g of oil/g of protein and a foam capacity of 76.67% [212]. The hydrolysis of viscera of *Pangasianodon hypophthalmus* with papain allowed obtaining hydrolysates with good solubility and foaming properties in a wide pH range [213].

The high protein content of fishery products makes it possible to use large factories for the production of their hydrolysates. Some works have even been reported in which a complete fish is used for this purpose, for instance, Cheng et al., (2020) used whole eel (*Anguilla marmorata*) and papain to obtain a hydrolysate with the potential to be used as a supplement in diets lacking protein due to the easy digestion of the peptide fractions obtained and its good technological properties such as an emulsion activity index (IAE) of 16.2 ± 1.22 and a stability index of the emulsion (ESI) of 1.44 ± 0.09 [214]. Also, with another eel (*Monopterus albus*) and using muscle, hydrolysates characterized by a high foaming capacity (>60%) with a stability greater than 30% were produced

[215]. The bonylip barb (*Osteochilus vittatus)* fillets were used for the elaboration of a protein hydrolysate of great nutritional value and with technological properties such as the absorption capacity of water (3.1 mL/g,) and oil (1.94 mL/g), emulsifying capacity (23.60%) and high water solubility (78.2%) [216]. Finally, using a mixture of papain and biduri plant extract, Witono et al., (2014) obtained hydrolysates from muscle of *Apogon albimaculosus* with high protein value (63-75%), high water retention capacity (89.01–103.32%) and great capacity for oil absorption (68.06 and 80.09%) [217].

In addition to the advantages described above, the use of papain to produce fish hydrolysates represents an advantage over the use of other proteases since the obtained hydrolysates have less bitter taste, a characteristic that broadens the possibilities of using these products in the food industry. The previous postulate was reported by Fan et al., (2019). They hydrolyzed frames of Alaska pollock (*Theragra chalcogramma*) with papain or other enzymes, and produced peptides with a reduction in the level of bitterness compared to the hydrolysates obtained with other four proteases [218].

2.3. Production of peptides with other bioactivities

Most of the studies carried out regarding the production of bioactive peptides from fish residues by hydrolysis with papain focuses mainly on antioxidant activity, as it happens with other enzymes such as Alcalase [34]. However, beyond the antioxidant activity there are other activities which are no less important. This section summarizes some works in this regard.

Dipeptidyl carboxypeptidase angiotensin I–converting enzyme (EC 3.4.15.1) which converts the inactive decapeptide angiotensin I into the potent vaso-constricting octapeptide angiotensin II, which plays an important role in the regulation of blood pressure and in the cardiovascular function, for this reason, many drugs used to treat hypertension focus on inhibiting this enzyme [219,220]. It has been reported that synthetic drugs used to treat hypertension have some serious side effects [221]. For this reason there is currently a growing interest in finding natural compounds that inhibit the angiotensin I–converting enzyme. In this sense, peptides with angiotensin I–converting enzyme inhibitory activity, obtained by enzymatic hydrolysis from different protein sources, emerge as a promising alternative to be used as nutraceuticals. Thus, angiotensin I-converting enzyme inhibitory peptides from loach (*Misgurnus anguillicaudatus*) were produced evaluating six different proteases, including papain [222]. Another study reports the generation and identification of angiotensin-I-converting enzyme inhibitory and antihypertensive peptides from boarfish (*Capros aper Linnaeus*) proteins by hydrolysis with papain, Alcalase and protease AP. The angiotensin-I-converting enzyme inhibitory activity of the 3-kDa boarfish protein hydrolysate generated using papain was 80% at a concentration of 1 mg/mL [223]. On the other hand, oven-dried and freeze-dried protein hydrolysates from fresh water fish (*Cirrhinus mrigala*) obtained using papain, had IC50 values for angiotensin I-converting enzyme inhibition of 1.15 and 1.53 mg of protein/mL, respectively. In addition, the angiotensin I-converting enzyme inhibitory activity of oven-dried protein hydrolysate was more stable during sequential digestion, suggesting that inhibitory activity was not affected by oven-drying [224]. Finally, Salampessy et al., reported the production of angiotensin I–converting enzyme inhibitory peptides from insoluble and soluble fish protein of leatherjacket (*Meuchenia sp.*) by using papain, bromelain or Flavourzyme [225]. Papain hydrolysates from insoluble fish protein gave two fractions, LP15 and LP16, having IC50 values for angiotensin I–converting enzyme inhibitory activity of 0.05 and 0.02 g/L, respectively [225].

Peptides obtained from fish residues by hydrolysis with papain have also been studied for their antimicrobial activity, to be used as preservatives in food as a natural and safe alternative to synthetic antimicrobials, whose use is usually restricted due to their potential toxic effects for the body [226]. In this regard, six proteolytic enzymes, among

them papain, were used to hydrolyze *Actinopyga lecanora* and the antibacterial activity of the hydrolysates was evaluated. Papain showed the highest degree of hydrolysis value (89.44%), and papain hydrolysate generated after 8 h hydrolysis showed an antibacterial activity against *S. aureus* of 20.19%, which was increased to 33.1% after fractionating using RP-HPLC [227]. In another study, papain hydrolysate from grass carp proteins showed an activity against *Listeria monocytogenes* of approximately 20% [228]. In addition, hydrolysates from skin and head of filefish (*Thamnaconus modestus*) were prepared by hydrolysis with different proteases (papain, trypsin, Neutrase, pepsin, and the mixtures of papain-Neutrase and mixture papain-trypsin). Results revealed that hydrolysates derived after 120 min of hydrolysis with trypsin, papain and the mixture papain-trypsin, were able to inhibit the growth of all tested bacteria (Gram-positive and Gram-negative strains), with different degrees of inhibition using the disc diffusion method [229].

Another important function of peptides is their ability to bind metals such as calcium, iron, and zinc, which are related to important basic biological processes, and their deficiency can cause many diseases [230–233]. In this context, some authors have reported the production of metal binding peptides from fish residues using papain in the hydrolysis process. For instance, collagen peptides with calcium-chelating ability from tilapia fish bone were prepared by papain hydrolysis under optimal conditions (4.5 h, pH 6.5, 62 °C, and enzyme to substrate ratio of 0.6%). Tilapia bone collagen calcium chelating peptide was a composed of small molecular peptides, where amino acids such as cysteine, serine, aspartic acid, glutamic acid, histidine, glycine, and lysine played an important role in the calcium chelating capacity of the active peptide [234]. In another interesting work, papain plus Flavourzyme were used to hydrolyze collagen from scales of *Lates calcarifer*, *Mugil cephalus*, *Chanos chanos*, and *Oreochromis* spp. to obtain peptides with Fe(II)-binding activity. It was found that collagen peptides from *Chanos chanos* showed the highest Fe(II)-binding activity, followed by those from *Lates calcarifer* and *Mugil cephalus*, and finally from *Oreochromis spp.* [235]. A somewhat different study, but which also takes advantage from the peptide binding function, is that reported by Grigore-Gurgu et al., who used bone tissue from phytophagous carp (*Hypophthalmichthys molitrix*) to obtain bioactive peptides through papain-assisted hydrolysis [236]. In this case, the objective was to evaluate the ability of these peptides to bind the flavonoids extracted from yellow onion skins, for their use in microencapsulation process. The results showed a binding value of 106 and also the presence of one single or one class of binding site during the interaction process of flavonoids with peptides. In the freeze-drying microencapsulation process, an efficiency for total flavonoids of 88.68 ± 2.37% was obtained [236].

Food surfactants, such as lecithin, are very important materials used for the preparation of food products like suspensions, emulsions and gels [237]. In this context, Zhao et al., reported the production of hydrolysates from cod bones by papain hydrolysis, which acted as a natural surfactant to synthesize high-stability bilayer nano-emulsions [238]. The average diameter of synthesized nano-emulsion with enzymatic hydrolysate could exhibit stability between 300 and 400 nm under a broad range of temperatures (30–90 °C), pH (4–8) and salt concentration (25–250 mM). In addition, the stability of emulsion lipid versus oxidation was enhanced by the absorbed peptides on the interface of the emulsion [238].

Obesity is a disarray of energy balance and primarily considered as a disorder of lipid metabolism in which pancreatic lipase is the key enzyme for the digestion of triglycerides; for this reason, the inhibition of this lipase prevents obesity [239,240]. In this regard, hydrolysates with anti-obesity activity (measured by the porcine pancreas lipase inhibitory rate) were prepared from fish water-soluble protein evaluating separately the enzymes papain, neutral protease and alkaline protease [240].

Prevention of circulatory system diseases such as arteriosclerosis is a subject of great importance [241,242]. In this sense, a study examined the effect of Alaska pollock meat protein hydrolysates prepared by

papain hydrolysis on cholesterol metabolism [243]. In rats fed, the hydrolysates diets were compared with casein diets with or without cholesterol and sodium cholate. The results show that the indexes of cholesterol metabolism-namely, triglyceride, serum cholesterol and low-density lipoprotein-cholesterol levels were significantly lower using the hydrolysates, whereas bile acid excretions and fecal cholesterol were higher [243].

Platelet activating factor acetylhydrolase enzyme is considered a promising therapeutic target for the prevention of atherosclerosis [244,245]. In this context, natural platelet activating factor acetylhydrolase inhibitory peptides were produced by papain hydrolysis of dried powder from red macroalga *Palmaria palmata*. After purification, a promising platelet activating factor acetylhydrolase peptide with an IC50 value of 2.32 mM and the amino acid sequence NIGK was obtained [246].

Finally, anti-anemia activity was reported by Dong et al., who used papain to hydrolyze protein from sea fish *Saurida elongate*. It was showed that the hydrolysate had a total percentage of eight essential amino acids as high as 41.5% of the total amino acids, and most importantly, the enzymatic hydrolysate was shown to contain significant in vivo anti-anemia activity on experimental anemia models induced by blood loss or cyclophosphamide damage to hematogenic mechanism [247].

2.4. Production of multifunctional peptides

Until this point in the review, the wide range of positive effects that papain can produce through hydrolysis in a huge variety of fish protein extracts and fish waste has been proven, giving and additional value to something previously considered as a residue. However, many studies focus just on one or two functional properties, while it is possible to find protein hydrolysates showing various functional activities at the same time. This section covers this kind of studies.

One example is a study where papain was employed to generate a fish protein hydrolysate from *Cirrhinus mrigala* that was dried in oven or in a freeze dryer [248]. The drying process did not affect to the free radical scavenging activity and linoleic acid peroxidation inhibition activity of the hydrolysates. The antioxidant properties in both OD-FPH and FD-FPH samples were reduced after a sequential digestion of the hydrolysates with pepsin and pancreatin. This way, the oven drying of fish protein hydrolysates may be advocated considering the properties and cost of production [248].

In another work, Murthy et al. isolated and characterized visceral proteases from little tuna (*Euthynnus affinis*), catla (*Catla catla*) and tilapia (*Oreochromis mossambicus*) [249]. Then, response surface methodology was employed to optimize the properties of the hydrolysate from croaker protein obtained by a mixture of crude tuna visceral waste enzyme and papain. A significant improvement was found for the hydrolysates free radical scavenging activity, ferric reducing antioxidant power, metal chelating activity, foaming capacity and foam stabilization capacity. A mixture of papain at 0.81% concentration and crude tuna visceral protease at 4.36% was found to be optimal [249].

Fish hydrolysates from threadfin bream (*Nemipterus japonicus*) waste were used to produce bioactive peptides using diverse proteases. Their properties were evaluated as a function of degree of hydrolysis. Except for functional properties of both hydrolysates, all the rest of the bioactive properties studied (antioxidant properties, radical scavenging activity, ferric reducing power and lipid peroxidation inhibition) of hydrolysates were improved with the increase in hydrolysis degree [250]. Papain, together with other proteases such as Alcalase or trypsin, has also been employed to study the effect of the produced blue-spotted stingray protein hydrolysates in metal chelating and radical scavenging activities, as well as protection against oxidative protein damage [251]. Different fractions were produced by membrane ultrafiltration. Alcalase proved to be the best enzyme to produce this kind of hydrolysates [251]. Eight different commercial enzymes, including papain, and their combinations were used to produce defatted salmon backbones hydrolysates

that showed antioxidant activity in vitro. Scavenging activity increased, while iron chelating ability decreased with increasing time of hydrolysis. All the hydrolysates showed angiotensin-I-converting enzyme inhibitory effect. Among the results of the study, it is interesting to remark that the papain + bromelain hydrolysates reduced the uptake of radio-labelled glucose into CaCo-2 cells, a model of human enterocytes, indicating a potential antidiabetic effect of the hydrolysates. A correlation was observed between the measured bioactivities, degree of hydrolysis and molecular weight profiles, supporting prolonged hydrolysis to maximize the peptides bioactivities [252]. It has also been reported that certain potent purified fractions of flying fish (*Exocoetus volitans*) backbone hydrolyzed by papain, pepsin and trypsin did not show any cytotoxic effect for Vero cell lines and exerted a significant antiproliferative effect on Hep G2 cell lines. In addition, the peptic protein hydrolysate showed maximum free radical scavenging potential and lipid peroxidation inhibition [253].

Finally, in another study, camel milk protein hydrolysates were produced using different proteases (Alcalase, bromelain, and papain) [254]. Then, different technological functions were compared between the hydrolysates and the native camel milk proteins. In this study, the highest hydrolysis degree was obtained when using papain. Antioxidant properties, radical scavenging activities and metal-chelating activity were enhanced with the hydrolysates. In real food model systems the inhibition of lipid peroxidation in fish mince and grape seed oil-in-water emulsion was higher employing papain than the other proteases [254].

3. Conclusions and future trends

Papain is an enzyme applied in the hydrolysis of fishery industry residues to produce bioactive peptides. As in many other instances, the combined used of papain with several other proteases provide hydrolysates with a higher hydrolyses degree and higher bioactivity [34,40].

However, for some reason, the application of this protease is not so widely spread as that of other proteases for the production of bioactive peptides, although the wide range of conditions where the enzyme may be utilized and its vegetal origin suggests that the enzyme should be applied with a higher intensity in this goal, even as part of proteases cocktails [205]. In some examples of this review where papain is compared to other proteases, papain is the best enzyme, while in others it is not so adequate, very likely as a consequence of the reaction conditions, presence of some uncontrolled compounds that can act as inhibitors, etc. It is foreseeable that in the near future, papain should be applied to a wider degree in this area. Moreover, papain, as many of the proteases used in the hydrolysis of proteins, is in most cases used in free form, and that way, it becomes incorporated to the final product. The use of immobilized papain may be a solution to this problem, as it has the advantage of an easy recovery and recycling of the enzyme [255]. Moreover, if properly performed, enzyme immobilization may be used to increase enzyme stability, enlarge the window of operation conditions, tuning selectivity and specificity, reducing inhibitions or even making enzyme purification possible [14–17,256]. The problem of using immobilized proteases for this goal is double: proteins are large substrates, and this makes only properly oriented enzymes active [22,41], and the reaction mixture may have some solids, making the use of standard porous supports hard (but it is possible to use nanoparticles [257] or magnetic porous supports) [258]. Papain immobilization used in this application should become more and more frequent in the next future.

CRediT authorship contribution statement

Veymar G. Tacias-Pascacio and Daniel Castañeda-Valbuena performed the initial literature search, all authors contributed to the writing and final editing of the paper. Veymar G Tacias-Pascacio and Roberto Fernandez-Lafuente designed the paper and supervised the writing.

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