Chapter 12
Biologically Active Compounds Form Seafood Processing By-Products

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12.1 Introduction

As in most food processing operations, seafood processing generates considerably high amount of waste as solid (carcasses, heads, viscera, skin) or liquid (blood, cleaning water). Thus, many large-scale seafood processing industries practise well-planned waste management system to avoid unnecessary environmental problems. The most common solid waste management system of seafood industries is recycling into fishmeal. However, continuously increasing seafood processing waste created wide-ranging discussion on effective utilization of fish processing waste. The necessity of an effective method to utilize the seafood waste arouses with over exploitation of marine resources. Recent advances in biotechnology and food processing have brought new paradigm to the classical way of processing waste by introducing a new avenue which generates a number of ingredients that can be used in food and pharmaceutical industries. Recent studies have identified a number of bioactive compounds from remaining waste materials. These ingredients possess a wide range of health-promoting abilities, including cure and prevention of a number of chronic diseases (Kim and Mendis 2006; Najafian and Babji 2012). Natural substances that have therapeutic values have attracted interest in diagnosis and therapy of various kinds of diseases in biomedicine since they exert a less number of side effects compared to that of synthetic origin. Moreover, awareness on added value of natural biologically active ingredients in modern society unwraps

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another growing market, nutraceutical and functional food (Myles 2003). Hence, this approach has opened up a potential way for processing seafood waste as natural health-promoting substances which have high commercial value.

12.2 Classical Way of Treating Seafood Waste

Seafood waste has been classified under the animal by-products and thus has to follow approved waste disposal methods. Under animal by-product category, seafood generates numerous waste materials that belong to several risk categories. Likewise, liquid wastes, including blood, are usually high in proteinaceous compounds and oils. These wastes have extremely high biochemical oxygen demand (BOD) and improper disposal may threaten the environment (Ababouch 2005). Therefore, practising traditional waste disposal methods have become increasingly restricted for seafood. Most of the approved seafood waste disposal methods are relatively expensive. In this regard, many large-scale processing operations tend to recover the waste disposal cost through conversion of the waste into value-added products. Most common waste-derived products are fishmeal and fish oil. Moreover, fish silage is another common waste product that is used as animal feed. In addition, converting waste into organic fertilizer is also practised (Arvanitoyannis and Kassaveti 2008). Although organic fertilizers generate little higher income than others, still all come under the category of low-value by-products. Further, increasing demand for seafood in modern society has steepened the problem by generating high amount of waste materials. Taking all into account, applying modern technological advances in seafood waste management to generate high-value ingredients would be an ideal solution.

12.3 Chitin and Chitosan from Seafood Waste

Crustacean shells and shellfish waste generated in seafood processing is one of the important waste materials. Efficient utilization of this waste material has become an environmental priority due to increased quantity as well as its slow natural degradation. The main structural component of these shells, chitin, has been identified as a potential target to be developed from these waste materials. Chitin is a long-chain polymer of *N*-acetylglucosamine (*N*-acetyl-2-deoxy-D-glucopyranose) units. This natural polymer can be easily processed into various kinds of derivatives which have range of biological activities. Chitin and its most common derivative chitosan have earned much attention as natural bioactive material with their nontoxicity, biocompatibility and biodegradability (Kim and Mendis 2006). Chitin can be simply extracted from shellfish waste with demineralization and deproteinization. The degree of deacetylation of chitin isolated in this way is around 0.1 %. The extracted chitin can be further deacetylated to a desired degree to produce chitosan.

Table 12.1 Examples of biological activities of chitin and its derivatives

Sample	Biological activity	Reference
Chitin oligosaccharide	Antioxidant	Ngo et al. (2008)
Chitin oligosaccharide	Anticancer	Huang et al. (2012)
Chitin nanoparticle	Anti-metastasis	Xu et al. (2012)
Chitosan sulphate	Anticoagulant	Fan et al. (2012)
Polysulphate chitosan	Antithrombin	Drozd et al. (2001)
Chitosan film	Antimicrobial	Dutta et al. (2009)
Chitin and chitosan	Immune enhancing	Harikrishnan et al. (2012)
Chitooligosaccharides	Anti-HIV	Artan et al. (2010)

Carboxymethyl derivative of chitin (CMC) is a water soluble form of chitin. CMC can be prepared by reacting chitin powder with monochloroacetic acid in isopropyl alcohol as a solvent using the condensation reaction (Jayakumar et al. 2010). Chitin and its derivatives possess various kinds of biological activities depending on their molecular weight, deacetylation and solubility. Hence, chitin and its derivatives have become popular in food and biomedical industries. However, applications of chitin and chitosan have faced some limitations with high viscosity and low solubility at neutral pH. Among the various means that have been explored to overcome this limitation, conversion of chitin and chitosan into their oligomers seems to be the best available option (Rinaudo 2006).

Several research articles have been published in peer-reviewed journals to reveal the biomedical and food industrial applications of chitin, chitosan and their oligomers (Table 12.1). Biodegradable, flexible and strong nature of chitin makes it possible to develop as surgical threads to be used in wound dressing. In addition, it has been shown that chitin possesses wound healing properties. Further, antibacterial and hemostasis properties of chitin that are necessary for wound healing provide additional benefits in order to cure wounds. Thus, biodegradable chitin wound dressings have added advantage over conventional dressing materials (Gupta et al. 2008). Moreover, chitin and chitosan are potent scavengers of oxidative radicals. Strength of radical scavenging activity of chitin and chitosan strongly depends on the molecular weight and degree of deacetylation. Low molecular weight chitosan oligomers with high deacetylation (90 %) have been recognized as potent scavengers. Further, it has been suggested that chitosan and its oligomers have an ability to act as scavengers of fat and cholesterol in digestive tract. It helps to reduce the low-density lipid level in liver and blood and provide hypocholesterolemic activity similar to those of dietary fibres (Prashanth and Tharanathan 2007).

Chitin and chitosan derivatives are capable of inhibiting tumour progression and cancer metastasis. In vitro and in vivo experiments have shown that low molecular weight chitosan potently inhibited cancer metastasis while improving immune functions. Thus, scientists believed that chitin and chitosan achieved the anticancer activity through immunostimulation. Further, several researchers have investigated the ability of chitosan as drug carrier. Chitin derivatives have shown fascinating ability to deliver certain drugs to the target place while maintaining its biodegradability. In the case of encapsulation, chitosan in the form of colloidal structure entraps various molecules and passes efficiently through mucosa and epithelia more. Moreover, nanoparticles made up of chitosan have also exhibited improved drug and protein delivery functions (Fuentes and Alonso 2012).

12.4 Hydrolysed Fish Proteins

Fish frames and offcuts generated from commercial fish filleting leave considerable amounts of muscle proteins which are nutritionally valuable and easily digestible with well-balanced amino acid composition (Harnedy and Fitzgerald 2012). In addition, specific degradation of remaining proteins results in biologically active protein hydrolysates and peptides which possess broad spectrum of health-promoting abilities. Since seafood is considered as prime source of proteins with high biological value, fish processing waste is an ideal and cheap source for extraction of valuable ingredients.

After removal of valuable portion, the remaining fish muscles are solubilized by means of several chemical and physical methods to obtain hydrolyzed fish proteins. Although fish protein hydrolysate (FPH) has classically been used for agricultural purposes, advanced technological developments make it possible to apply the FPH as functional ingredients in food and pharmaceuticals. Likewise, the hydrolysate is also a rich source of biologically active small peptides that have been proven for various therapeutic potentials. Hydrolysis of protein is achieved through acid-, alkali- or enzyme-mediated breakdown of parent proteins in the waste into smaller protein fractions, peptides and free amino acids. Acid hydrolysis makes the product unpalatable due to tryptophan destruction and the formation of sodium chloride after the neutralization. Alkaline hydrolysis produces some toxic compounds which are undesirable for human consumption. Among protein hydrolysis methods, enzymatic hydrolysis offers several advantages over others (Kristinsson and Rasco 2000).

Proteolytic enzymes come from several sources, such as plant (papain, ficin, bromelain), animal (trypsin, pancreatic enzymes) or microbial (Pronase, Alcalase), are employed for hydrolysis depending on the type of processing waste and the desired functionality of end product. In conventional enzymatic method, commercial enzymes are directly applied under predefined conditions such as pH, temperature, incubation time and enzyme/substrate ratio (Bhaskar et al. 2008). Fermentation approach of producing fish protein hydrolysates is not a novel concept. Proteases producing microbial strains are used as starter culture and incubated in preferred conditions to grow microbes on fish processing waste. Physicochemical as well as functional properties of enzymatic hydrolysate vary with the degree of hydrolysis which determines size of protein fractions. Over hydrolysis may impair some functional properties of food proteins or may develop off-flavours in hydrolysates (Balti et al. 2010). Further, improvement of functional properties and therapeutic value of protein hydrolysate could be obtained through a selective molecular weight cutoff. An ultrafiltration membrane system equipped with a molecular cutoff has been identified as an effective method to purify protein hydrolysates based on molecular weight of protein factions (Jeon et al. 1999). Serial enzymatic digestions in a system

Table 12.2 Bioactive fish protein hydrolysates from seafood wastes

Fish source	Bioactivity	Reference
Pacific hake	Antioxidant	Samaranayaka and Chan (2008)
Brownstripe red snapper	Antioxidant	Khantaphant et al. (2011)
Ornate threadfin bream	Antioxidant	Nalinanon et al. (2011)
Cod	ACE inhibitor	Jeon et al. (1999)
Round scad	Antioxidant	Thiansilakul et al. (2007)
Yellowfin sole	Anticoagulant	Rajapakse et al. (2005)
Blue whiting	Satiating effect	Cudennec et al. (2012a, b)
Blue whiting	Anti-proliferative	Picot et al. (2006)

of multistep recycling membrane reactor combined with ultrafiltration membrane system have been developed to produce protein hydolysates with desired molecular weights while preserving expensive photolytic enzymes (Byun and Kim 2001).

12.4.1 Bioactivities of Fish Protein Hydrolysates

The main goal of digesting protein leftover into FPH is to improve the functional properties of the original protein molecules. This improvement of functional properties accompanies with advanced health-promoting abilities due to improved functionality achieve through high amount of polar groups, solubility of hydrolysate and their bioavailability. Thus, several studies have been carried out to prove various kinds of biomedical applications of FPHs (Table 12.2). In particular, FPH possesses potent antioxidant activity which attenuate oxidative damages taking place in the body where endogenous antioxidant defence mechanism is not enough. As an economically viable product, FPHs seem good candidates to combat with production of superoxide anion (O^{2-}) and hydroxyl (OH^{1-}) radicals which are considered as causative agents for the initiation of chronic diseases such as heart disease, stroke, arteriosclerosis, diabetes and cancer (Perera and Bardessy 2011). The advantage of the product is providing protection against oxidative damage while providing an additional nutritional value. Additionally, protein hydrolysates generated from fish processing waste reduce risk of cardiovascular diseases (CVD) by triggering several key process associated with the disease, including blood clot and platelet formation, angiotensin I-converting enzyme activity and cholesterol metabolism. Moreover, a recent study (Cudennec et al. 2012a, b) has demonstrated that FPH derived from blue whiting suppresses appetite via enhanced cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) secretion in in vitro STC-1 cells as well as in vitro experiment. The biological effects of CCK and GLP-1 stimulation lead to promising effect on body weight reduction which has gained much attention in developed countries. All these findings clearly point out that FPHs have potential of disease risk reduction. Thus, identified potential sources are currently used in production of biologically active FPHs in the form of nutraceutical and functional food.

12.5 Biologically Active Peptides

Peptides with small backbone are generated through digestion of various means, and these peptides are capable of playing an important role in metabolic regulations. Therefore, several scientific articles have highlighted that small peptides have potential to use as nutraceuticals and functional foods (Shahidi and Zhong 2008). During the investigation of biological consequence of FPHs, it was apparent that small peptides present in the hydrolysates mediate biochemical pathways to exert defined health property of the hydrolysates. Detailed studies revealed that small protein fragments containing 3–20 amino acids residues showed this potent activity, and the activity and its extent strictly depended on amino acid composition, sequence and molecular weight. Before hydrolysis, the peptides remain latent within the parent protein, and released by hydrolysis allow them to exercise hormone-like physiological effect in the body. (Himaya et al. 2012). It is well known fact that protein hydrolysis method and types of proteinase employed are crucial factors for biological activity of the peptide. The ultrafiltration membrane system has been identified as a useful tool to purify active peptides based on molecular weight. Sequential enzymatic digestion with different enzymes has been employed to achieve desired functionality of peptides (Kim et al. 2007). Biological activities of peptides derived from fish processing waste range from simple antioxidant activity to prevention and cure of serious chronic diseases such as cancer.

Several studies have reported that peptides derived from fish proteins showed antihypertensive activity by inhibiting the activity of angiotensin I-converting enzyme (ACE) which plays a vital role in regulation of blood pressure. ACE participates in the body's renin-angiotensin system by converting inactive angiotensin I into an active vasopressor angiotensin II. This conversion increased the blood pressure which triggered the function of blood vessel dilator bradykinin (Huang et al. 2005). After the discovery of critical role of ACE in blood pressure regulation, several commercial ACE inhibitors, such as captopril, enalapril, alacepril and lisinopril, were synthesized and employed to treat hypertension and heart failures. Among the natural ACE inhibitors that have been isolated from various food and natural sources, fish processing by-products derived ACE inhibitors are of great interest due to preferred sequence of peptides for the potent inhibition of ACE (Lee et al. 2010). In addition, several peptides which possess significant impact on causative agents of chronic disease have been isolated. Table 12.3 summarizes the biologically active peptides isolated from different sources of fish proteins.

12.6 Collagen and Gelatin from Fish Waste

Collagen has earned much interest as a biomaterial in medical applications due to its biodegradability and weak antigenicity. Among several collagens, Type I collagen is the most naturally abundant collagen in animal and found in skin, tendon, vascular ligature, organs and bone. Collagen is composed of three similarly sized triple helix polypeptide chains which consist of around 1,000 amino acids residues.

Table 12.3 Biological activities of peptides derived from fish muscle proteins

Fish source	Amino acid sequence	Biological activity	Reference
Alaska pollock	Leu-Pro-His-Ser-Gly-Tyr	Antioxidant	Je et al. (2005)
Croaker	Thr-Phe-Cys-Gly-Arg-His	Antioxidant	Nazeer et al. (2012)
Tuna fish	VKAGFAWTANQQLS	Antioxidant	Je et al. (2007)
Tuna fish	Gly-Asp-Leu-Gly-Lys-Thr-Thr-Thr-Val-Ser-Asn-Trp-Ser-Pro-Pro-Lys-Try-Lys-Asp-Thr-Pro	ACE inhibition	Lee et al. (2010)
Yellowfin sole	Met-Ile-Phe-Pro-Gly-Ala-Gly-Gly-Pro-Glu-leu	ACE inhibition	Jung et al. (2006a, b)
Alaska pollock	Val-Leu-Ser-Gly-Gly-Thr-Thr-Met-Ala-Met-Tyr-Thr-Leu-Val	Ca binding	Jung et al. (2006a, b)
Blue whiting	NA[a]	Cholecystokinin release	Cudennec et al. (2008)

Gelatin is structurally different form of the same macromolecules which make collagen and particularly a hydrolysed form of collagen. Common sources of collagen and gelatin, bovine hide, pig skin or chicken waste, have faced some constrains related to biological contaminants and religious issues (Aberoumand 2010). Mainly this reason sought an alternative source for collagen and gelatins for commercial purposes. Raw materials from fish waste have received considerable attention in recent years as an alternative for collagen and gelatin extraction due to its unique features. Fish skin and bones have been mainly used for collagen extraction, and three main extraction methods, neutral salt solubilization, acid solubilization and enzyme solubilization, have been used based on the characteristics of waste and end product. During extraction, triple helix structure which contributes to the unique properties of collagen should be preserved. To prepare fish gelatin, extracted which collagen is solubilized with hot water treatment by breaking down the hydrogen and covalent bonds of the triple helix, resulting in helix-to-coil transition and conversion into soluble gelatin (Guillén et al. 2011).

Several unique applications of fish by-product-derived collagen and gelatin have been reported due to enriched properties of fish collagen (Table 12.4). High hydroxyproline content of collage has resulted in reduced pain in osteoarthritis patients supplemented with collagen/gelatin hydrolysate (Moskowitz 2000). Collagen shows great advantages as a carrier molecule of drug, protein and gene through long-term maintenance of the concentration and controlled release at target sites. Moreover, collagen serves as a main scaffold for biotechnological applications. Detailed studies revealed that collagen type I, with selective removal of its telopeptides, exhibited characteristic features of bio-scaffold for bone regeneration. Experimental data confirmed that fish by-product-derived collagen and gelatin have inherent properties of collagen and can be used as an alternative to mammalian products (Senaratne et al. 2006). In addition, enzymatic hydrolysis of fish collagen and gelatin produces small peptides which have potent biological activities. Repeated Gly-Pro-Ala sequence of

Table 12.4 Biological activities of fish collagen and gelatin

Fish source	By-product	Biochemical potential	Reference
Rohu and Catla	Type I collagen	High thermal stability	Pati et al. (2010)
Nile tilapia	Collagen drink	Attenuate UVA damage	Kato et al. (2011)
Nile tilapia	Peptide	Free radical scavenging	Ngo et al. (2010)
Alaska pollock	Peptide	ACE inhibition	Byun and Kim (2001)
Pacific cod	Peptide	Antioxidant and ACE inhibition	Ngo et al. (2011)
Unicorn leatherjacket	Gelatin film	Antimicrobial	Ahmad et al. (2012)
Chum salmon	Peptide	Memory enhancement	Pei et al. (2010)

gelatin peptides has reinforced the peptide with high antioxidant and antihypertensive properties. Numerous studies have been conducted to reveal the biological activity of fish collagen- and gelatin-derived peptides.

12.7 Fish Bones as a Mineral Source

Commercial fish filleting from large as well as small fish result in huge amount of fish bones which is generally discarded as a waste. Fish frame account for approximately 10–15 % of total fish biomass. The bones are mainly composed of calcium phosphate and collagen protein with some special carbohydrates and lipids. Thus, the waste could be used as mineral source for food and biomedical industries while giving an added value to fish processing by-products. Fish bone consists of 60–70 % of inorganic substances, mainly calcium phosphate and hydroxyapatite (Toppe et al. 2007). Hydroxyapatite (HA)- and calcium phosphate-related ceramic material have earned much attention in various biomedical applications due to their close similarity to composition of natural bones. In particular, the composition [Ca_{10} $(PO_4)_6$ $(OH)_2$] and Ca/P molar ratio of HA are more similar to inorganic part of bone and teeth, and hence, this biological HA could be used as an implant material for orthopaedic and dental applications. Even though much effort has been paid to obtain synthetic hydroxyapatite, fish bone provides a cheap source for extraction of biological HA with preserved chemical characteristics and many advantages (Boutinguiza et al. 2012). Pallela et al. (2011) have developed polymer-assisted thermal calcination method to isolate micro- and nanostructured HA form tune (*Thunnus obesus*) bones. Further, findings proved that HA isolated with polymer-assisted method shows less toxicity and high biocompatibility. In addition, high level of calcium in fish bone indicates that it would be useful as a potential source to obtain calcium for dietary supplements. As most of the regular diets are calcium deficient, several calcium supplementations have been commercialized. Nevertheless, bioavailability of calcium of these products is not clearly studied. It is well known fact that small fish is a good source of balanced calcium, and fish-derived calcium is readily absorbed into human body. Thus, bones from fish processing waste can be used to produce fortified products with high biological value, and several convenient methods have been developed to soften the fish bone to convert it into an edible form.

12.8 Omega-3 Fatty Acids

Cold water oily fish, such as salmon, herring, mackerel, anchovies, and sardines, and fish oil derived from these fish have been recognized as well-balanced sources of omega-3 fatty acids, especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Due to enhanced health benefits of omega-3 fatty acids, world fish consumption has reached to a level which threatened the marine fish sources, and thus, fishing for oil extraction is not encouraged. Fish processing by-products have been identified as an ideal candidate for extraction of fish oil rich in omega-3 fatty acids while giving a positive insight into sustainable marine fisheries (Immanuel et al. 2009). The processing leftovers, such as head, skin and internal organs, are rich sources of omega-3 fatty acids, and method and conditions for the extraction are determined base of the nature of fish source. Presently, several methods, such as high-speed centrifugation, Soxhlet extraction, low-temperature solvent and supercritical fluid extraction, are employed to extract fish oil. Among them, wet reduction followed by pressing and centrifugation is the most common method used to produce fish oil from waste materials (Chantachum et al. 2000). Purification of omega-3 fatty acids from extracted fish oil is a challenge due to the presence of complex mixture of triacylglycerols and vulnerability of free fatty acids EPA and DHA to oxidize into hydroperoxides. A recent study shows that enzymatic deacidification of high-acid crude fish oils is an effective approach to extract high amount of n-3 fatty acids (Wang et al. 2012).

The inverse relationship between high level of omega-3 fatty acids present in bold and chronic disease has been reported in several studies. Findings suggest high levels of EPA and DHA in blood which in turn reduced rate of coronary heart diseases have an association with inhibition of lipid-rich atherosclerotic plaques growth, reduction in formation of thrombus, improving vascular endothelial function and lowering blood pressure (Lavie et al. 2009). Moreover, there is evidence for therapeutic value of omega-3 fatty acids. For instance, beneficial effects against diabetes mellitus, anti-inflammatory action and thereby protection against autoimmune diseases and potent activity against human carcinomas including prostate, lung, colon and breast have been reported. Basically, documented health benefits of fish oil are a result of high content of EPA and DHA, and fish processing by-product-derived oil fall under the agreement of expected fatty acid composition for biomedical treatments (Byun et al. 2008; Wu and Bechtel 2008).

12.9 Other Constituents

Internal organs, fish egg, scales, eyeball and blood have been identified as the other potential sources of high-value biological constituents which have considerable market value. Fish internal organs, especially viscera, are a rich source of digestive enzymes, proteases and lipases (Khantaphant and Benjakul 2010). As marine organisms have adopted for extreme condition prevalence in the marine environment, these enzymes have unique characteristics, including higher catalytic efficiency at low temperatures, lower sensitivity to substrate concentrations, greater stability at broader pH range and stability under high temperatures (50–60 °C) (Klomklao 2008). Owing to the special properties, these enzymes have broad applications in biomedical industry as a biocatalyst. Wound debridement, treatment for blood clots, antibiotic therapy and treatment for inflammation are classical examples of protease-based medical treatments (Seabra and Gil 2007). Furthermore, several studies reported that fish digestive enzymes are a cheap source to extract enzymes that could be used to produce biologically active peptides from different protein sources.

Fish egg derived from large-scale fish processing industries has been identified as a potential source of lectin, a naturally occurring sugar binding protein. Due to its high specificity and ability to form stable complexes with carbohydrates, it may be used as antibiotic to detect and inactivate activity of pathogens (Jung et al 2003, Jimbo et al. 2007). Hyaluronic acid is an interesting compound isolated from fish eyeball. This polymer has repeating units of *N*-acetyl-D-glucosamine and glucuronic acid and exists as cartilage in tissues. In recent years, hyaluronic acid has gained interest as an ingredient of cosmeceutical and pharmaceutical. Eyeball of certain fishes contains significant amount of hyaluronic acid which can be extracted with high purity (99.5 %) for clinical and cosmetic applications (Murado et al. 2011).

12.10 Concluding Remarks

Seafood usage has reached to a level which threatens the marine ecosystem. Several reports have highlighted that half of marine resources have been overexploited. Thus, identification and exploration of sustainable means to produce seafood have become a prioritized requirement of current seafood research. Recycling of seafood waste seems to be a positive approach to increase the utilization of existing seafood resources. However, commercial value of classical seafood by-products discourages the use of waste materials. Identification of biologically active materials and their potential application in growing fields, such as biomedical, nutraceutical and functional food, have brought a new insight to fish processing by-products. Thus, comprehensive studies on identified potential ingredients and development of commercially viable processing methods for isolation and extraction will facilitate a successful journey of fish processing by-products in the biomedical field. This seems to be an ideal approach to overcome constraints associated with conventional seafood waste management.

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