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Mini Review

Bioactive peptides from fish by-products with anticarcinogenic potential

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Abstract

As a major cause of death, cancer has affected the world population, both directly and indirectly. There are however, growing numbers of cancer cases some of which could be prevented or even treated using natural compounds. Bioactive peptides from terrestrial and marine environment have been claimed to potentially reduce the risk of chronic diseases or maintain health. Fish processing industry produces more than 50% by-products which can be converted into valuable fish protein hydrolysate (FPH) by chemical or biochemical hydrolysis. This paper discusses the potency of fish by-products as sources of bioactive peptides with anticarcinogenic potential. Moreover, a short review about the antioxidant and anticancer activities of novel bioactive peptides isolated from fish by-products is presented.

Introduction

According to the 2014 Food and Agriculture Organization (FAO) Fisheries and Aquaculture Department's report, world per capita fish consumption increased significantly from an average of 9.9 kg in the 1960's to 19.2 kg in 2012. Fish (including finfish, molluscs and crustaceans) currently represents about 16.6% of animal protein supply and 6.5% of all protein for human consumption with the value of exported products reaching US$136 billion (FAO Fisheries and Aquaculture Department, 2014). An increasing demand for fish products means greater volumes of fish processing by-products are generated. Fish waste or fish by-products are identified as leftovers that are not saleable in general but can be recycled after treatment or processing (Kim and Mendis, 2006). This includes viscera, heads, cut-offs, bone, skin, fins, roes and frames.

Fish by-products present a huge problem for environment and seafood industry. The amount of fish discarded by seafood industries vary within 50-75% of the total weight of the catch, depending on species, size, season and fishing ground (Rustad *et al*., 2011). In 2005, Food and Agriculture Organization reported significant decrease of fishery discards due to increased utilization of unwanted by-products (Kelleher, 2005). The utilization of fish by-products is an important production opportunity for the fishing and seafood processing industry, as it can potentially generate additional income as well as reduce disposal costs for these materials (Arvanitoyannis and Kassaveti, 2008). The most common approach in utilizing fish-by products is by converting unused fish parts into fish protein hydrolysate (FPH). Research on hydrolysis of fish protein has been developed from early 1960's with the main objective to provide cheap nutritious fish protein for developing countries or to accelerate animal feed production (Kristinsson and Rasco, 2000). Fish protein hydrolysates possess desirable functional properties and a high nutritional value. They contribute to water-holding, texture, gelling, foaming and emulsification properties in different food systems (Rustad *et al*., 2011).

Fish protein hydrolysate can be produced by hydrolysing fish muscle or body parts using chemicals (acid or alkaline), or biochemical (microbial enzymes, digestive enzymes) added at appropriate levels in controlled systems (Ovissipour *et al.*, 2012). The quality or properties of peptides liberated by FPH is highly dependent on the type of proteases or chemicals, temperature, pH and time implemented during hydrolysis (See *et al*., 2011; Nazeer and Anila Kulandai, 2012). Protein hydrolysate usually consists

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of small fragments of bioactive peptides that contain 2-20 amino acids though some have been reported to be more than 20 residues (Ryan *et al.*, 2011). Bioactive peptides are inactive within the sequence of the parent proteins and may be released by hydrolysis or digestion (Sarmadi and Ismail, 2010). After digestion and being absorbed in the intestines, bioactive peptides enter the blood stream and reach the target sites (e.g. liver, colon) to exert the bioactivities (Erdmann *et al*., 2008). Several studies showed that bioactive peptides derived from fish by products may exert more than one physiological effect in human body (Je *et al*., 2009; Naqash and Nazeer, 2011).

Rodrigues *et al.* (2009) suggested that bioactive peptides with lack of toxicity to healthy cells would be a promising candidate for anticancer treatment. Peptide-based drug therapies are also known for their strong specificity, tumor penetrating ability due to their small size (Barras and Widmann, 2011). Anticancer peptides (ACPs) act against cancer cells through several mechanisms including: (1) cytoplasmic membrane disruption via micellization; (2) induction of apoptosis, and (3) interaction of peptides with cell surface gangliosides (Huang *et al.*, 2011). Numerous researches showed that these ACPs are obtainable from various food proteins, particularly milk (Gill and Cross, 2000) and marine species (Zheng *et al*., 2011; Suarez-Jimenez *et al.*, 2012). Interestingly, recent reports have also demonstrated that fish by-products can be used as valuable sources of ACPs (Picot *et al*., 2006; Alemán, Pérez-Santín, Bordenave-Juchereau *et al.*, 2011). This review, therefore, will illustrate the recent advances of utilization of fish by-products as sources of novel bioactive peptides with anticarcinogenic potential.

Cancer and bioactive peptides from marine origin

Cancer is a leading cause of death worldwide. An estimated 14.1 million people were diagnosed with cancer across the world in 2012, with more than 8.2 million people dying from the disease (Ferlay *et al*., 2015). In Australia, over 43,000 people have died from cancer in 2012. It is also predicted that 1 in 3 Australians will be diagnosed with cancer by the age of 85 (Cancer Council Australia, 2015). Disturbingly, the number of cases of cancer diagnosed in Australia is projected to rise for both males and females and is expected to reach about 150,000 in 2020—an increase of almost 40% from 2007 (Australian Institute of Health and Welfare, 2012). Cancer is also notorious for its high cost of treatment. Recently, the Cancer Council Australia (2015) reported that $4.5 billion in direct health system were dedicated to covering cancer treatment costs.

The cause of cancers and how to prevent, treat or cure them has continually become the major topic in biomedical research and publications. Cancer can be defined as a group of diseases characterized by uncontrolled division and spread of abnormal cells (American Cancer Society, 2015). Whilst cell division is a normal physiological process that occurs in tissues, disruption of balance between cell proliferation and apoptosis may cause certain mutations in DNA and lead to cancer (Gerl and Vaux, 2005). Carcinogenesis or cancer development may occur in three stages, i.e. initiation, promotion and progression (Weston and Harris, 2003). It can be triggered by external factors (tobacco inhalation, chemicals, food contamination, and radiation) and internal factors (hormones, immune system damage, inflammation and physical conditions) (Anand *et al*., 2008). While several cancers are associated with infectious organisms and parasites (Oliveira *et al*., 2007), it is also increasingly evident that genetic background can affect individual's susceptibility to carcinogens (Spitz and Bondy, 2006).

Cancer is mostly treated by surgery, or in some cases combined with chemotherapy and radiotherapy (American Cancer Society, 2015). However, such therapies often are associated with deleterious effects caused by drug-induced damage to healthy cells and tissue (Hubenak *et al*., 2014). Thus discovery of new safe cancer drugs becomes an important goal of research in biomedical sciences, with increasing number of new anticancer compound to be sourced from the marine environment (Jimeno *et al*., 2004; Simmons *et al*., 2005; Zheng *et al*., 2011). In 2010, an economic analysis estimated the value of anti-cancer drugs of marine origin at US $563 billion to 5.69 trillion, with 55 to 214 new compounds sourced mostly from Phyla Chordata, Mollusca, Porifera, Bryozoa, Proteobacteria and Cyanobacteria (Erwin *et al*., 2010).

As anticancer drugs, marine anticancer peptides (MACPs) induce cancer cell death through different mechanisms (Figure 1). Apoptosis, a programmed cell death, is the most preferable way of cancer cell death during treatment (Zheng *et al.*, 2011). Apoptotic process can be triggered by p38 mitogen-activated protein kinases (MAPK) by inhibiting pro-survival gene Bcl-2 and induce pro-apoptotic gene Bax (Yip and Reed, 2008) or by activating Jun N-terminal kinase (JNK) and MAPK that lead to the release of cytochrome c (Cyt C) from mitochondria (Shieh *et al*., 2010). MACPs disrupt the tubulin-microtubulin equilibrium by inhibiting cell mitosis by binding to the protein tubulin and preventing polymerization into the microtubules (Islam and

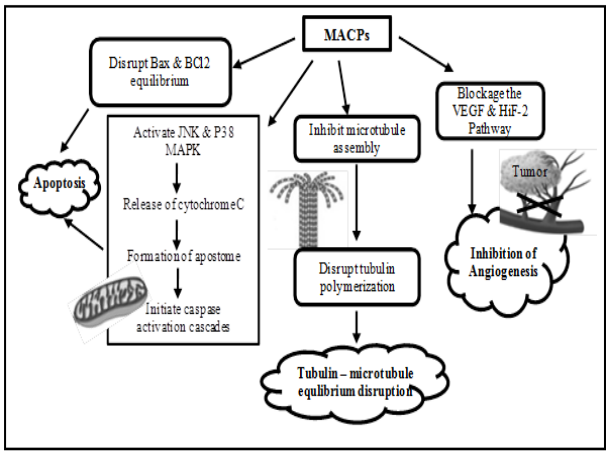

Figure 1. Depiction of mechanisms of marine anticancer peptides (MACPs) in inducing cell cancer death (Adapted from Zheng *et al.*, 2011)

Iskander, 2004). Eventually, essential cellular functions, such as chromosome segregation and cell tumour maintenance will be affected (Hadfield *et al.*, 2002). Angiogenesis or the formation of new blood vessels plays important role in the growth of tumours. Inhibition of vascular endothelial growth factor (VEGF) and hypoxia inducible factor 2 alpha (HIF2α) pathway by peptides directly inhibited tumor cell growth (Weidemann and Johnson, 2008).

Anticancer peptides from fish by-products

Most marine-derived anticancer peptides have been isolated from molluscs, tunicates, ascidians and sponges (Suarez-Jimenez *et al*., 2012), while a number of anticancer studies involving fish by-products has been limited (Table 1). Cancer growth inhibitory activity was observed from peptides extracted from sepia ink oligopeptides. The peptide, identified as N Gln-Pro-Lys with a molecular mass of 343.4 Da, inhibited the proliferation of human prostate cancer (DU-145) cells (Ding *et al*., 2011). The antiproliferation activity was probably due to the presence of proline and lysine in the peptide sequence. Roomi *et al*., (2015) reported that nutrient mixture (NM) contained proline and lysine proved to be highly toxic for DU-145 cells. Furthermore, two antiproliferative peptides contained proline (Leu-Pro-His-Val-Leu-Thr-Pro-Glu-Ala-Gly-Ala-Thr and Pro-Thr-Ala-Glu-Gly-Gly-Val-Tyr-Met-Val-Thr), isolated from tuna dark muscle, also showed potential inhibitory activity on the growth of breast cancer (MCF-7 cells) (Hsu *et al*., 2011). Certain amino acids, however, behaved differently toward various cancer cell lines. Gu *et al*., (2015) reported that Cys promoted the proliferation of gastric cancer (GC) cells as well as breast cancer (BC). Asp and Arg stimulated the growth of BC while Glu induced the apoptosis of GC cells. Interestingly, Ala treatment showed opposite effects on the proliferation and of GC cells and BC cells, suggesting that Ala may be the key functional amino acid in different cancer metabolisms.

Peptides derived from snow crab by-products showed anticancer activity on colon, breast, prostate and lung cancer cell lines (Doyen *et al*., 2011). A promising anticancer peptide was also obtained from shrimp shells and was shown to significantly inhibit the growth of both colon and liver cancer cells (Kannan *et al.*, 2011). Recently, small molecular size peptides (< 3 kDa) isolated from Flathead by-products was reported to inhibit the growth of HT-29 colon cancer cells up to 91.04% (Nurdiani *et al.*, 2017). The profiles of most anticancer peptides isolated from fish by-products, however, were not yet identified or characterised so that the mechanism of anticancer activity of these peptides are largely unknown. In addition, despite the fact that peptides derived from fish by-products showed promising cancer cell growth inhibitor activity (Picot *et al.*, 2006), the cytotoxicity effect of these peptides on normal cells were rarely discussed. Thus, further cell based and *in vivo* studies are required to ensure the efficacy and safety of anticancer peptides derived from fish by-products.

Radicals scavenging peptides from fish by-products

Cancer as well as many human diseases, including ischemia, diabetes, arthritis, can be triggered by excessive production of free radicals or reactive oxygen species (ROS) (Najafian and Babji, 2012). Several experimental studies suggested that ROS can act as both initiators and promoters of tumors by damaging cellular macromolecules such as DNA, proteins, and lipids, and by acting as cell-signaling molecules, in the form of nitric oxide (Benedetti *et al*., 2015). Furthermore, critical illness can drastically increase the production of ROS or reactive nitrogen species (RNS) (Abiles *et al*., 2006). Fortunately, high level of an antioxidant (>66% of recommended dietary intake) could reduce the risk for worsening oxidative stress by 94%, regardless of change in severity of illness (Abiles *et al.* , 2006).

Antioxidants occur naturally in food and peptides with antioxidant activities have been identified from a number of aquatic species (Bernardini *et al.*, 2011). In regards to fish by-products, several peptides with high antioxidant and/or free radicals scavenging activities are well-documented (Table 2). Generally, peptides with high free radical scavenging activity contain amino acids with sulfur-containing side chains (Cys and Met), aromatic side chains (Trp, Tyr, His and Phe) or hydrophobic amino acids (Val,

Table 1. Anticancer activities of peptides isolated from fish by-products

Fish species	By products used	Enzyme used/Treatment	Reported activities	Cell line used	Sequence of isolated peptide	Reported mode of action	Reference
Atlantic salmon (*Salmo salar*), Atlantic cod (*Gadus morhua*), Plaice (*Pleuronectes platessa*), Blue whiting (*Micromesistius poutassou*), Atlantic emperor (*Lethrinus atlanticus*), Pollack (*Pollachius pollachius*) and Portuguese dogfish or siki (*Centroscymnus coelolepis*)	Fresh filleting by-products or headed and gutted by-catches	pH-shift extraction method, Protamex and Alcalase	Antiproliferative	breast cancer cell lines	-	Cancer cell cytotoxicity	(Picot *et al.*, 2006)
Chum salmon (*Oncorhynchus keta*)	Skin gelatin	Alcalase, Papain and Neutrase	Cell proliferation, cycle progression and apoptosis	hFOB1.19 cells lines	-	Weak 17b-estradiol-like effect and could elevate cell viability	(Fu and Zhao, 2013)
Flying fish (*Exocoetus volitans*)	Backbone	Papain, Pepsin and Trypsin	Antiproliferative	Hep G2 cell lines	-	Cancer cell cytotoxicity	(Naqash and Nazeer, 2011)
Langostino lobster (*Pleuron- coides planipes*), shrimp (unknown species), shrimp (*Peneaus setiferus*)	Shells	Cryotin	Antiproliferative	human colon (Caco-2) and liver (HepG2) cancer cells	-	Cancer cell cytotoxicity	(Kannan *et al.*, 2011)
Sepia (*Sepia esculenta*)	Ink	Trypsin	Antiproliferative	DU-145 cells	N Gln-Pro-Lys (343.4 Da)	Cancer cell cytotoxicity	(Ding *et al.*, 2011)
Snow crab	**By-products (cephalothorax shells, digestive systems including hepatopancreas, and physiolog-ical liquid)**	**Protamex**	**Anticancer**	**colon (HTC15), breast (BT549), prostate (PC3) and lung (A549) cancer cell lines**	**-**	**Cancer cell cytotoxicity**	**(Doyen *et al.*, 2011)**
Tuna	Dark muscle	Papain and Protease XXIII	Antiproliferative	human breast cancer cell line MCF-7	Leu-Pro-His-Val-Leu-Thr-Pro-Glu-Ala-Gly-Ala-Thr (1206 Da) and Pro-Thr-Ala-Glu-Gly-Gly-Val-Tyr-Met-Val-Thr (1124 Da)	Cancer cell cytotoxicity	(Hsu *et al.*, 2011)

Leu and Ala) (Batista, 2013, Ngo *et al*., 2014). Je *et al*., (2005), for example, identified a sequence of high antioxidant peptide (Leu-Pro-His-Ser-Gly-Tyr) from Alaska pollack (Theragra chalcogramma) frame protein hydrolysate. Peptides contained Leu, Pro and Gly were also reported to act as a good electron donor and could react with free radicals to convert them to more stable products and terminate the radical chain reaction (Jaiganesh *et al*., 2011; Chi *et al*., 2015).

Beside amino acid composition, the antioxidant nature of FPH is highly dependent on peptide size and disruption of tertiary structure of parent protein by hydrolysis (Elias *et al*., 2008). The type of substrate, type of protease, and conditions implemented during hydrolysis influence the degree of hydrolysis of FPH as well as molecular weight of peptides produced (Sun, Shen and Luo *et al*., 2011). As proteases have specific cleavage positions on polypeptide chains, fish protein hydrolysate may contain different mixtures of high, medium or low molecular weight peptides with various bioactivities (Nasri *et al.*, 2013). Several authors reported that high antioxidant activity was inversely related to molecular weight (Je *et al*., 2007; Yang *et al*., 2009; Hsu, 2010; Sabeena Farvin *et al*., 2014) as low molecular weight peptides interacted more effectively with radicals, thus interfering with the oxidation process (Wang *et al*., 2012). This was contracted by Alemán, Giménez, Pérez-Santin *et al.*, (2011) who reported a direct relationship – higher molecular weight exerted a greater ABTS activity, which was attributed to a large number of free amino acids and small peptides without antioxidant capacity.

In order to further examine the protective effect of peptides against reactive oxygen species, several researchers performed cell-based studies. Mendis, Rajapakse, Byun *et al.* (2005), for instance, investigated antioxidant activities of jumbo squid skin gelatine by assessing two purified peptides (Phe–Asp–Ser-Gly-Pro-Ala-Gly-Val-Leu and Asn-Gly-Pro-Leu-Gln-Ala-Gly-Gln-Pro-Gly-Glu-Arg) on cultured human fibroblast cells to overcome tert-butyl hydroperoxide-mediated oxidative cell death. The study showed that both peptides exhibited a dose-dependent cell viability enhancement effect. Similarly, purified peptides from skate (Okamejei kenojei) exhibited an inhibitory activity against the elevation of intracellular ROS in the activated cells. The peptide sequence was found to be Met-Val-Gly-Ser-Ala-Pro-Gly-Val-Leu and Leu-Gly-Pro-Leu-Gly-His-Gln (Ngo *et al*., 2014). In order to prove the efficacy and safety of antioxidative peptides, further cell based as well as *in vivo* studies are required.

Table 2. Free radical scavenging activities of peptides isolated from fish by-products

Fish species	By products used	Enzyme used/ Treatment	Reported radical scavenging activities	Sequence of isolated peptide	Reported mode of action	Reference
Alaska pollack (*Theragra chalcogramma*)	Frame	Mackerel intestine crude enzyme (MICE)	Hydroxyl	Leu-Pro-His-Ser-Gly-Tyr (672 Da).	Chelating and lipid radical-trapping ability of the imidazole ring of His. Tyr is a potent hydrogen donor.	(Je *et al.*, 2005)
Alaska pollack (*Theragra chalcogramma*)	Skin	Neutrase, Flavourzyme, Alcalase, Trypsin, Protamex and Papain	2,2-diphenyl-1-picrylhydrazyl radical (DPPH)	-	-	(Jia *et al.*, 2010)
Bigeye snapper (*Priacanthus macracanthus*)	Skin gelatin	Pyloric caeca extract	DPPH, 2, 2-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS)	-	Peptides acted as hydrogen donors	(Phanturat *et al.*, 2010)
Bigeye tuna (*Thunnus obesus*)	Head	Alcalase	DPPH, hydroxyl, superoxide	-	The peptides acted as potent electron donors.	(Yang *et al.*, 2011)
Bigeye tuna (*Thunnus obesus*)	Dark muscle	Alcalase, α-chymotrypsin, Neutrase, Papain, Pepsin, andTrypsin	DPPH, hydroxyl, superoxide, and alkyl	H-Leu-Asn-Leu-Pro-Thr-Ala-Val-Tyr-Met-Val-Thr-OH	Peptides acted as electron donors, scavenged the cellular radicals and enhanced the viability of tert-butyl hydroperoxide-induced cytotoxicity.	(Je *et al.*, 2008)
Black Pomfret, (*Parastromateus niger*)	Viscera	Pepsin, Trypsin, and α-chymotrpsin	DPPH	Ala-Met-Thr-Gly-Leu-Glu-Ala (701.9 Da)	Peptides acted as electron donor	(Jaiganesh *et al.*, 2011)
Black scabbardfish (*Aphanopus carbo*)	By products	Protamex	DPPH	-	Active peptides transformed radicals to more stable products	(Batista *et al.*, 2010)
Bluefin leatherjacket (*Navodon septentrionalis*)	**Heads**	**Papain**	**DPPH, ABTS, superoxide and hydroxyl**	**Trp-Glu-Gly-Pro- Lys (WEGPK), Gly-Pro-Pro (GPP), and Gly-Val-Pro-Leu-Thr (GVPLT)**	**Antioxidant activities are due to small molecular peptides and the hydrophobic and/or aromatic amino acid residues in their sequences.**	**(Chi *et al.*, 2015)**
Catla (*Catla catla*) and Rohu (*Labeo rohita*)	Visceral waste	Alcalase, Neutrase, Protex 7L, Protease-P-amano	DPPH	-	-	(Hathwar *et al.*, 2011)
Channa striatus* and *Lates calcarifer	Roe	Alcalase	DPPH	-	Donation of a proton, stabilise and or termination of free radicals.	(Galla *et al.*, 2012)
Cobia (*Rachycentron canadum*)	Skin	Alkali-aided hydrolysis, Bromelain, Papain, Pancreatin, and Trypsin	DPPH	-	Peptides acted as potent electron donors.	(Yang *et al.*, 2008)
Cod (*Gadus morhua*)	Backbones	Protamex	DPPH	-	Peptides donated hydrogen to radicals, resulting in formation of more stable alcohols and peroxides and reduced oxidation of liposomes.	(Šližyte *et al.*, 2009)
Flying fish (*Exocoetus volitans*)	Backbone	Papain, Pepsin and Trypsin	DPPH, superoxide and hydroxyl Antiproliferative effect on Hep G2 cell lines	Leu-Glu-Val-Lys-Pro (596.9 Da)	Peptide inhibit the radical-mediated peroxidising chain reaction by increasing solubility of peptides in lipid	(Naqash and Nazeer 2011; Shabeena and Nazeer 2011)
Hoki (*Johnius belengerii*)	Skin gelatin	Trypsin, α-chymotrypsin, and Pepsin	DPPH and superoxide	His-Gly-Pro-Leu-Gly-Pro-Leu (797 Da)	Peptides acted as potent electron donors.	(Mendis, Rajapakse, Byun *et al.*, 2005)
Hoki (*Johnius belengerii*)	**Frame**	**pepsin, trypsin, papain, α-chymotrypsin, Alcalase and Neutrase**	**DPPH, hydroxyl, superoxide radicals Hydroxyl-radical-induced DNA damage protective properties.**	**Glu-Ser-Thr-Val-Pro-Glu-Arg-Thr-His-Pro-Ala-Cys-Pro-Asp-Phe-Asn (1801 Da)**	**Peptides decreased t-butylhydroperoxide-induced cytotoxicity on human embryonic lung fibroblasts and protected induced DNA damage.**	**(Kim *et al.*, 2007)**
Horse mackerel (*Magalaspis cordyla*)	Viscera	In vitro gastrointestinal digestion	DPPH and hydroxyl	Ala–Cys–Phe–Leu	Leu and Ala reacted highly to the hydrophobic PUFA	(Sampath Kumar *et al.*, 2011)
Jumbo squid (*Dosidicus gigas*)	Skin gelatin	Trypsin, α-chymotrypsin, and Pepsin	Hydroxyl and carbon-centered Oxidation-induced cell viability	Phe–Asp–Ser–Gly–Pro–Ala–Gly–Val–Leu (880.18 Da) and Asn–Gly–Pro–Leu–Gln–Ala–Gly–Gln–Pro–Gly–Glu–Arg (1241.59 Da).	Antioxidant activities are due to hydrophobic amino acids present in peptide sequences	(Mendis, Rajapakse and Kim, 2005)
Nile tilapia (*Oreochromis niloticus*)	Scale gelatin	Alcalase, pronase E, trypsin and pepsin	DPPH, hydroxyl radical and superoxide Hydroxyl-radical-induced DNA damage protective properties	Asp-Pro-Ala-Leu-Ala-Thr-Glu-Pro-Asp-Pro- Met-Pro-Phe (1382.57 Da)	Peptides acted as potent electron donors and inhibited the oxidative damage of DNA.	(Ngo *et al.*, 2010)
Pacific cod (*Gadus macrocephalus*)	Skin gelatin	Alcalase, Neutrase, Papain, Trypsin, Pepsin, and α-chymotrypsin	2′,7′-dichlorofluorescin diacetate and oxidation-induced DNA damage in mouse macrophages (RAW 264.7 cells)	Thr-Cys-Ser-Pro (388 Da) and Thr-Gly-Gly-Gly-Asn-Val (485.5 Da)	Peptides acted as potent electron donors and inhibited the oxidative damage of DNA.	(Ngo *et al.*, 2011)
Sardinelle	Heads and/or Viscera	Crude enzyme from *Mustelus mustelus* intestines, crude enzyme from viscera of sardinelle (*S. aurita*), hepatopancreas of cuttlefish and	DPPH	-	Peptides acted as potent electron donors.	(Barkia *et al.*, 2010)

Sardinelle (*Sardinella aurita*) by-products	Heads and viscera	Alcalase, crude enzyme from Aspergillus clavatus ES1, alkaline proteases from B. licheniformis NH1, crude enzyme from viscera of sardine (*Sardina pilchardus*)	DPPH	Leu-His-Tyr, Leu-Ala-Arg-Leu, Gly-Gly-Glu, Gly-Ala-His, Gly-Ala-Trp-Ala, Pro-His-Tyr-Leu and Gly-Ala-Leu-Ala-Ala-His.	Peptides acted as potent electron donors	(Bougatef *et al.*, 2010)
Seela (*Sphyraena barracuda*) and Ribbon Fish (*Lepturacanthus savala*)	Backbone	Papain, Pepsin and Trypsin	DPPH and hydroxyl radicals scavenging activity	-	-	(Nazeer *et al.*, 2011)
Shrimp	Heads	Autolysis	DPPH	-	Carotenoproteinsacted as singlet oxygen quenchers.	(Sowmya *et al.*, 2011)
Silver carp (*Hypophthalmichthys molitrix*)	Processing by-product	pH-shift method, Alcalase, Flavourzyme, Neutrase, Papain, Pepsin, Protamex, and Trypsin	DPPH , hydroxyl and superoxide Alleviate H2O2-induced oxidative stress in human intestinal epithelial Caco-2 cells.	-	Peptides acted as potent electron donors.	(Zhong *et al.*, 2011)
Skate (*Okamejei kenojei*)	Skin gelatin	Alcalase, flavourzyme, Neutrase and Protamex	Protective effects in human umbilical vein endothelial cells	Met-Val-Gly-Ser-Ala-Pro-Gly-Val-Leu (829 Da) and Leu-Gly-Pro-Leu-Gly-His-Gln (720 Da)	Purified peptides scavenged intracellular ROS	(Ngo *et al.*, 2014)
Skipjack (*Katsuwana pelamis*)	Roe	Alcalase	DPPH, ABTS and superoxide anion	Asp-Leu-Asp-Leu-Arg-Lys-Asp-Leu-Tyr-	Peptides acted as potent electron donors	(Intarasirisawat *et al.*, 2013)
Tilapia	Skin gelatin	Thermal hydrolysis	DPPH	-	Antioxidative activity was associated with oligopeptides obtained after hydrolysis.	(Yang *et al.*, 2009)
Tilapia (*Oreochromis niloticus*)	Frame Protein	Properase E, Pepsin, Trypsin, Favourzyme, Neutrase, Gc106 and Papain	DPPH, superoxide anion radical, hydrogen peroxides and hydroxyl radical	Asp-Cys-Gly-Tyr (456.12 Da) and Asn-Tyr-Asp-Glu-Tyr (702.26 Da)	Tyr served as hydrogen donors	(Fan *et al.*, 2012)
Tuna	Backbones	Alcalase, a-chymotrypsin, Neutrase, Papain, Pepsin and Trypsin	DPPH, hydroxyl, superoxide	Val-Lys-Ala-Gly-Phe-Ala-Trp-Thr-Ala-Asn-Gln-Gln-Leu-Ser (1519 Da)	Peptides acted as potent electron donors	(Je *et al.*, 2007)
Tuna	Liver	Alcalase, Neutrase Protamex, and Flavourzyme	DPPH, hydroxyl, superoxide Hydroxyl-radical-induced DNA damage protective properties	-	Peptides acted as potent electron donors	(Ahn *et al.*, 2010)
Tuna	Dark muscle	Orientase and Protease XXIII	DPPH	Leu–Pro–Thr–Ser–Glu–Ala–Ala–Lys–Tyr (978 Da) and Pro–Met–Asp–Tyr–Met–Val–Thr (756 Da)	Peptides scavenged radicals by donating protons. Tyrosine residue is a significant source of hydrogen.	(Hsu, 2010)
Tuna (*Katsuwonus pelamis*)	Liver	Flavourzyme, Alcalase, Protamex, and Neutrase	DPPH, hydroxyl, hydrogen peroxide Oxidative DNA damage protective activity	-	Peptides acted as antioxidants due to their electron donating ability. Protective activity against hydroxyl radical-induced DNA damage on pBR322 plasmid DNA	(Je *et al.*, 2009)
Tuna, Halibut and Jumbo flying squid	Skin and tunic	Alcalase Collagenase, Trypsin, Pepsin	ABTS	-	Free radicals scavenging activity related to the amino acid compositions of the gelatins.	(Alemán, Giménez, Montero *et al.*, 2011)
Walleye Pollock (*Theragra chalcogramma*)	Skin	Trypsin and Flavourzyme	DPPH, superoxide anion radical, hydroxyl radical and hydrogen peroxide	-	Hydrophobic amino acids acted as electron donors and could react with free radicals.	(Zhuang *et al.*, 2009)

Conclusion

This review discussed the potential of fish by-products as natural sources of bioactive peptides with antioxidant and anticancer properties. Based on evidence of potential health benefits, bioactive peptides derived from fish by-products have promising applications as natural nutraceuticals. Until now, however, a limited number of cell-based as well as *in vivo* studies on antiproliferative and antioxidant activity of peptides from fish by-products have been performed to date. Further research on utilization of fish by-products for treatment and management of cancer is essential in order to improve our understanding about its mechanism and application.

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