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Review Article

MARINE FISH-DERIVED BIOACTIVE PEPTIDES AND PROTEINS FOR HUMAN THERAPEUTICS

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ABSTRACT

In recent years, much attention has been paid to the existence of peptides with biological activities and proteins derived from foods that might have beneficial effects for humans. Fishes are rich sources of structurally diverse bioactive compounds. The importance of fish as a source of novel bioactive substances is growing rapidly. Marine fish is a major source of high-quality peptides, proteins, lipids, and a wide variety of vitamins and minerals. Marine fish-derived bioactive peptides based on their structural properties and their amino acid composition and sequences, in addition to nutrient utilization, these peptides may be involved in various biological functions and including inhibition of angiotensin-I-converting enzyme (ACE) and and antioxidant and immunomodulatory, antimicrobial and and anticoagulant activities. Development of bioactive peptides from fish proteins and their health promoting ability is increasing. Protein and bioactive peptides from marine fish may promote the production of potentially lead to promising therapeutic applications. Marine fish usually find extensive use as therapeutic and diagnostic proteins. This review paper highlights the important functions and therapeutics potentials of Marine Fish-derived Bioactive Peptides and Proteins for human therapy.

Keywords: Marine fish, Bioactivities, Proteins, Peptides, Human therapeutics

INTRODUCTION

Marine bioresources produce a great variety of specific and potent bioactive molecules including natural organic compounds such as fatty acids, polysaccharides, polyether, peptides, proteins, enzymes and lectins. Proteins from marine sources show promise as functional ingredients in foods because they possess numerous important and unique properties such as film and foaming capacity, gel forming ability and antimicrobial activity [1]. Bioactive peptides usually contain 3–20 amino acid residues and their activities are based on their amino acid composition and sequence [2]. These peptides are reported to be involved in various biological functions such as antihypertension, immunomodulatory, antithrombotic, antioxidant, anticancer and antimicrobial activities, in addition to nutrient utilization [2, 3].

The holistic approach to link medicine and diet has ascertained that the fish. Because of the presence of specific biochemical ingredients in addition to their nutritive values, fish have a positive impact on an individual's health including his physical well-being and mental state. Fish also contains some health-promoting components beyond the traditional nutrients serve to prevent diseases. Fish is a low fat and/or good source of protein, essential for the healthy growth and maintenance of muscles and body tissues. Fish offer scope for use as functional food and as sources of nutraceuticals. Great amount of marine fish species have been identified with potential nutraceutical and medicinal values. Consequently, a number of bioactive compounds have been identified including fish muscle proteins, peptides, collagen, gelatin, fish oil and fish bone. Some dietary proteins of fish cause specific effects going beyond nutrient supply. Bioactive peptides derived from various fish muscle proteins have shown various biological activities including antihypertensive, antibacterial, anticoagulant, anti-inflammatory, and antioxidant activities, and hence they may be a potential material for biomedical and food industries.

Fish can serve as a source of functional materials, such as polyunsaturated fatty acids, polysaccharides, minerals and vitamins, antioxidants, enzymes and bioactive peptides. Fish is a fabulous food lots of variety in taste and texture, versatile and low in saturated fat. It's also low in calories-the perfect healthy diet food. Marine fish is a major source of high-quality protein, lipids, and a wide variety of vitamins and minerals. These macromolecules and their derivatives show different pharmacological activities, which make the fish as a therapeutic diet. Modern technology has made it easy to explore the therapeutic importance of fish-based diet on cardiovascular diseases, neurodegenerative diseases, radicals-mediated diseases, and cancer. Among the complementary and alternative medicine (CAM) approaches used by Americans, natural products are the most popular. Recent interest in natural diets that can protect health has resulted in foods that have functionality from the nutritional point of view. A Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases met in Geneva from 28 January to 1 February 2002 has adopted a resolution regarding the primary and secondary prevention of chronic diseases and the reduction of their impact [4].

In this review, focus on exploration of proteins their derivatives from marine fish as a major source for bioactive compounds and their biological activities and potential applications as ingredients in functional foods, nutraceuticals, and pharmaceuticals and their functional role in healthcare. A few fish nutraceuticals and functional ingredients have been highlighted.

Fish Protein Resources

Currently, two-thirds of the total food fish supply is obtained from capture fisheries in marine and inland waters, while the remaining one-third is derived from aquaculture. Fish contributes up to 180 kcal per capita per day, but reaches such high levels only in a few countries where there is a lack of alternative protein foods grown locally or where there is a strong preference for fish (Iceland, Japan and some small island states). More typically, fish provides about 20-30 kcal per capita per day. Worldwide, about a billion people rely on fish as their main source of animal proteins. Dependence on fish is usually higher in coastal than in inland areas. About 20% of the world's population derives at least one-fifth of its animal protein intake from fish, and some small island states depend almost exclusively on fish.

These days, the world's population gets about 25% of its protein from fish. Above 60% population gets 40% animal protein from fish in third world. It has been calculated that fish provide about 55% of all the animal protein consumed in Asia [5]. The protein calories of fish in average is 8-21 g/100g and proteins of fish have a high biological value. The per capita fin-fish demand was around 13.7 kg in 2010 and expected to go up to 14.3 kg in 2015. By 2030, annual fish consumption is likely to rise to some 150-160 million tonnes, or between 19-20 kg per person [6].

Fish is a rich source of easily digestible protein. Fish proteins are highly sensitivity to proteolytic digestion, with a digestibility of more than 90%. The *in vivo* digestibility of proteins of raw fish meat is in the range 90–98%. The enhanced digestibility is mainly due to the absence of strong collagenous fibers and tendons in fish muscle, which are common in land animals. PER of fish proteins is slightly above that of casein—the major milk protein. Evidently, the protein quality of most fish may exceed that of meat or are equal to that of an ideal protein such as lactalbumin [7].

Fish Protein In Healthcare

Fish proteins are rich in all the essential amino acids (particularly methionine and lysine) in contrast to most proteins from plant sources, which lack adequate amounts of one or more essential amino acids. The nutritive value of marine fish proteins is equal to or better than that of casein and red meat proteins because of their favorable essential amino acid pattern [8]. There are no significant differences in the amino acid composition of freshwater and marine fish. However, certain marine fish such as mackerel and tuna may be exceptionally rich in the amino acid histidine. With the increasing knowledge of the functional properties of fish protein hydrolysates, there are many researchers are conducting studies on the developments and applications of fish-derived functional foods and nutraceuticals.

Recently, much attention has been focused on the identification and characterization of the structure, composition and, sequence of bioactive peptides. Biologically active peptides play an important role in metabolic regulation and modulation. These peptides can be used as functional food ingredients, or nutraceuticals and pharmaceuticals to improve human health and prevent disease. Bioactive peptides isolated from various fish protein hydrolysates have shown numerous bioactivities such as antihypertensive, antithrombotic [9-11], anticoagulant [12], immunomodulatory and antioxidative activities [12, 13].

1. Fish protein supplements

Fish protein Concentrate (FPC) is the cheapest animal protein supplement available in the market. Early studies on nutritive value of fishery products started with fish protein concentrate (FPC), developed during the 1950s to solve the problem of malnutrition among poor sections of world population, FPC has been well examined as a protein supplement in a variety of foods. When 37% of conventional dietary protein was replaced with FPC, the metabolic balance of calcium, phosphorus, nitrogen, and fluoride were not affected, suggesting feasibility of replacing one-third of daily protein with FPC. Since collagen is a pure protein containing 7 of the 8 essential amino acids, it has many applications as a protein supplement [14]. It can be added either to diet or supplement formula to readily increase the protein in a meal or drink to provide optimal nutritional support. As a supplement to the staple diet, FPC has high-quality protein and is inexpensive.

2. Fish protein powders

Protein powders from fish such as threadfin bream, lizardfish, and purple-potted bigeye fish were prepared by drying surimi from these fish species. The resulting products contained 73% protein and 17% carbohydrate (from the cryoprotectant added during surimi preparation). The powder obtained by spray drying of the solution had 65% protein and as much as 24% carbohydrate [15]. Soluble protein powders were also made from by-products of processing of Alaska pollock, namely, viscera, liver, heads, trimmings, and frame and were evaluated for their functional, nutritional, and rheological properties. The fish protein powder is also good sources of potassium, phosphorus, magnesium, and amino acids [16, 17]**.** A comparison with Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) 1990 recommendations showed that these powders were good sources of all the essential amino acids [15-17].

3. Fish protein hydrolyzates

The fish protein hydrolyzates (FPHs) have an excellent solubility and possessed functional properties that are governed by their concentrations. Proximate compositions of FPHs are in the range 1–8% moisture, 81–93% protein, 0–5% fat and 3–8% ash. Antioxidant activities of protein hydrolyzates from Yellow stripe trevally (*Selaroides leptolepis)* prepared using Alcalase 2.4 L (HA) and Flavourzyme 500 L (HF) with a DH of 15% by pH-stat method were determined. The antioxidant activities of both hydrolyzates were stable when heated at 90°C for 10 and 30 min and subjected to a wide pH range (2–12). Freeze-dried FPH from herring containing 77–87% proteins with a DH ranging from 10 to 18% was reported to have a significant antioxidant activity. Fish hydrolyzate can be used as a protein supplement for use of populations that ingest low-protein diets such as those based on wheat, rice, or corn. Fish collagen is produced from the skins of wild deep-sea ocean fish such as cod, haddock and pollock. This collagen hydrolysate acts a therapeutic agent of potential utility in the treatment of Osteoarthritis and osteoporosis [18], also use of collagen hydrolysate for patient with Osteoarthritis [19]. Fish protein hydrolysates have attracted much attention of food biotechnologists due to the availability of large quantities of raw material for the process, and presence of high protein content with good amino acid balance and bioactive peptides (antioxidant, antihypertensive, immunomodulatory and antimicrobial peptides) [20].

4. Development of bioactive peptides from fish proteins

Use of fish, especially the marine fish for antibiotics and pharmacologically active compounds has received ever increasing interest. Among fish-derived bioactive peptides and proteins those obtained from marine source are known in particular [2, 21]. The functional properties of fish proteins may be improved by the use of specific enzymes and by choosing a defined set of hydrolysis conditions [22]. Numerous effects have been made after *in vitro* and animal trials for bioactive peptides and proteins, such as immunomodulating, antihypertensive, osteoprotective, antilipemic, opiate, antioxidative and antimicrobials and a range of therapeutic products derived from marine fish are as follows:

4.1. Fish-derived bioactive peptides

Recent research has shown that marine fishes are rich sources of bioactive peptides. The potential of providing bioactive compounds such as peptides also make fish proteins important in human nutrition and health management. During digestion of food proteins, a wide range of bioactive peptides is produced. Low-cost fish can be good sources of bioactive peptides [23-25]. A mild procedure for obtaining lipipeptic and peptidic fractions from abundantly available sardine (*Sardina pilchardus*) has been reported [26, 27]. Partially digested protein hydrolyzate produced by the action of commercial proteinase, alcalase, on cooked sardine (*S. pilchardus*) meat could be a source of peptides. The bioactive peptides can also work indices of fish quality [28]. Fish collagen peptide, when orally administrated, can repair damaged cartilage and can have synergistic effects with N-acetyl glucosamine [29].

4.2. Calcium-binding activity

Binding of minerals such as calcium and iron can help in their absorption in the gut. Skeleton from industrial processing of Hoki (*Johnius belengerii*) was digested by heterogeneous enzyme extracted from intestine of Bluefin tuna. The tissue enzyme could biodegrade the Hoki bone matrices composed of collagen, non-collagen proteins, carbohydrate, and minerals. A fish bone phosphopeptide (FBP) containing 23.6% of phosphorus was isolated. The FBP had a molecular weight of 3.5 kDa and could bind calcium without the formation of insoluble calcium phosphate. It was suggested that the produce could be used as a nutraceutical with a potential calcium-binding ability [30]. Peptide from collagen and gelatin hydrolyzates can also have functional properties. A fish commercial collagen hydrolyzate, Peptan F, has been found to enhance protein quality and flavor characteristics of beverages [31]. Jung *et al.,* 2005 [32] reported that fish peptides are also capable of accelerating calcium absorption.

4. 3. Fish bone peptide as calcium supplements

There have been many studies on alternative calcium-rich diet or Ca supplements other than the most common and trusted milk. Among them, teleost fish like anchovy and mola, which are commonly consumed in Asian countries, could be an important Ca dietary supplement, especially in population groups with low intakes of milk and dairy products [33]. The beneficial effects of marine teleost fish bone peptide (FBP) for Ca bioavailability as calcium supplements for bone mineralization.

4.4. Obesity control

Obesity is a risk factor for many diseases, including heart disease, high blood pressure, diabetes [34], and some cancers. Certain bioactive peptides have been shown to contribute to weight management. Eating more lean animal proteins can assist in successful weight loss. If you follows a calorie restricted diet, you may be in need of good quality protein so the body doesn't burn it as energy (the body should burn the fat). And fish can do the trick and not provide the heavy amount of saturated fats like red meat. Plus the calories in fish are lower. A specific casein peptide, glycomacropeptide (GMP) plays a significant role in appetite suppression. It stimulates the production of cholecystokinin, an intestinal hormone, which induces the sensation of satiety [35].

4.5. Beneficial for diabetic patients

Dietary fish protein in subjects with insulin resistance as showed that cod protein prevents the development of insulin resistance in rats. Dietary fish protein may also enhance insulin sensitivity in overweight insulin-resistantsubjects by improving a primary defect in insulin signaling to PI 3-kinase, leading to reduced activation of the downstream effectors Akt and PKC. To determine whether this is the case, we will study the effects of fish protein on insulin sensitivity in humans, and how it improves the ability of muscles to use glucose. Such studies will help to advise individuals with insulin resistance or type2 diabetes about eating fish. A study was aimed at examining the therapeutic effects of marine collagen peptides (MCPs) from fish hydrolysate in Chinese patients with type 2 diabetes mellitus (T2DM). Significantly reduced levels of fasting blood glucose, human glycated hemoglobin A1c (GHbA1c), fasting blood insulin, total triglycerides, total cholesterol, low-density lipoprotein, and free-fatty acids, but increased levels of insulin sensitivity index and HDL were observed in T2DM patients following treatment with MCPs for 1.5 and 3 months [36].

4.6. Fish protein as potential antioxidants

Fish proteins contain antioxidative activity and some functional properties [37, 38]. Recently, a number of studies demonstrated that protein hydrolysates derived from fish proteins are potential sources of antioxidant peptides and several antioxidant peptides from these protein hydrolysates have been isolated [39-42]. The bioactive antioxidant peptide Leu-Gly-Leu-Asn-Gly-Asp-Asp-Val-Asn, isolated from Conger eel (*Conger myriaster*), exhibited high levels of antioxidant activity [43]. Nalinanon *et al*., 2010 [44] isolated peptides with antioxidant properties from the muscle of Ornate threadfin bream by skipjack tuna pepsin. These authors found that the highest scavenging activities for ABTS and DPPH were obtained whit protein hydrolysates with 20% DH. Antioxidant active of peptides from fish gelatins has been reported. Peptides derived from tryptic hydrolyzate of Hoki (*Johnius belengerii*) skin gelatin exhibited significant scavenging activities on superoxide, carbon-centered DPPH radicals as assessed by electron spin resonance spectroscopy. Peptide from Croaker (*Otolithes ruber*) muscle protein hydrolysate was purified, characterized and evaluated for its *in vitro* and *in vivo* antioxidant activity. Results showed that purified peptide contained the amino acid sequence as Lys-Thr-Phe-Cys-Gly-Arg-His (861.6 Da), which contribute to its antioxidant activities. This peptide efficiently quenched 1,1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radicals (84.5 ± 1.2 and 62.4 ± 2.9%), and successfully inhibits the lipid peroxidation and DNA damage and proven to be a potent antioxidant at different *in vitro* systems [45]. Gelatin peptide from fish waste can have antioxidant activity [42].

4.7. Fish antimicrobial peptides

Like other organisms, fish exude different types of antimicrobial peptides (AMPs), which are positively charged short amino-acid-chain molecules involved in host defense mechanisms. The early discovered AMPs from fish, such as the Red Sea Moses sole (*Pardachirus marmoratus)*. Zhang *et al*. 2004 [46], found an antimicrobial component in the skin homogenate of *Epinephelus fario* using a trypsin digest. The antimicrobial protein was purified by ion-exchange and gel-filtration chromatography. Fish antimicrobial peptides can be used as antibacterial, antiviral, antifungal, immunomodulatory and antitumor agents [47]. Almost all fish antimicrobial peptides have antibacterial or bacteriostatic functions against several Gram-negative and -positive strains. Su, 2011 [48] isolated and identified a novel 20-residue antimicrobial peptide, pelteobagrin, from the skin mucus of yellow catfish with the amino acid sequence GKLNLFLSRLEILKLFVGAL. Pelteobagrin exerted broad-spectrum activity against a wide range of bacteria without hemolytic activity. Huang *et al*., 2007 [49] showed that tilapia TH2–3 is similar to the Japanese flounder (*Paralichthys olivaceus*) 26-amino acid peptide JF2, tilapia TH2–2 is similar to Japanese flounder 19-aa JF1, and tilapia TH1–5 is similar to Sea bream (*Chrysophrys major*) hepcidin.

4.8. Angiotensin I-converting enzyme inhibitory (antihypertensive) activity

Marine fish-derived bioactive peptides can be developed as antihypertensive components. Angiotensin-converting enzyme (ACE) plays a crucial role [50]. ACE is an exopeptidase (a dipeptidyl carboxypeptidase, EC 3.4.15.1) that plays a fundamental role in blood pressure homeostasis as well as fluid and salt balance in mammals. The first marine ACE inhibitory peptide was isolated from sardine, which was hydrolyzed by Denazyme AP, a protease from *Aspergillus oryzae*. Later, ACE inhibitory peptides have been isolated from hydrolyzates of various other fishery sources. These include salmon, sardine, yellowfin sole, and dried bonito [51]. Salmon muscle hydrolyzate has been observed to be a potent inhibitor of ACE and exhibited an antihypertensive effect when administered orally to spontaneously hypertensive rats [51]. An alkaline protease-derived ACE-inhibitory peptide from sardine showed C50 (concentration for 50% inhibition) value of 1.63 μM for inhibition of ACE. In some cases, enzymatically hydrolyzed fish skin gelatin have shown better biological activities compared to the peptides derived from fish muscle proteins to act as antioxidants and antihypertensive agents [9]. The hydrolyzed offal protein could significantly inhibit the decrease in red blood cells, hemoglobin, and platelets [52]. Besides ACE inhibitory activity, peptides from cod, salmon, and trout proteins also inhibited prolyl endopeptidase (EC 3.4.21.26) [53].

4.9. Inhibit cancer metastasis

Cancer cells that metastasize to other parts of the body grow new blood supplies and eventually overcome the person's organ systems. Polar fish, such as northern cod, express glycoproteins that are rich in the (Thomsen-Friedenreich disaccharide) TFD antigen, which protect them from freezing. The research team developed a special form of TFD, called TFD100, purified from Pacific cod. The TFD100 binds to galectin-3, a protein that is overexpressed in prostate cancer cells, and blocks its interaction with the TFD antigen found on the surface of the cells. Galectin-3 (gal3) enables cancer cells to adhere to the walls of blood vessels and also kills activated T-cells, a type of white blood cell, which helps the cancer cells to spread throughout the body and evade the immune system. The TFD100 prevents cancer cells from attaching to the vessel walls, suppresses T-cell death and boosts the immune response."Because the gal3-TFD interaction is a key factor driving metastasis in most epithelial cancers, this high-affinity TFD100 should be a promising anti-metastatic agent for the treatment of various cancers, including prostate adenocarcinoma [54].

4.10. **Immunostimulant activity**

Both fish sauce and fish silage are protein hydrolyzates with immune stimulating properties. *In vitro* and *in vivo* studies have shown that certain peptide fractions in FPHs may stimulate the nonspecific immune defense system. Generally, fish sauce is regarded as a typical Asian product made from tropical fish species, but ancient literature reveals that fish sauce was a common food product in southern Europe more than 2000 years ago. Recent studies have shown that it can also be made from cold water species [23].

4.11. Antithrombin

Antithrombins from Atlantic salmon (*Salmo salar*) and Rainbow trout (*Oncorhynchus mykiss*) have been isolated, which functions *in vitro* as does its human counterpart. The inactivation of thrombin by salmonid antithrombin, which was dependent on heparin concentration was maximal at pH 7.8–8.4 and maximal at concentrations between 1.5 and 6 units/mL. Unlike the human system, the salmonid thrombin–antithrombin interaction functions over a wide range of temperatures and were present at temperatures as low as 3°C [55].

4.12. Calcitonin

Hormone obtained from Salmon helps to regulate calcium and decreases bone loss. For osteoporosis patients, taking Salmon calcitonin, which is 30 times more potent than that secreted by the human thyroid gland, inhibits the activity of specialized bone cells called osteoclasts that absorb bone tissue. This enables bones to retain more bone mass. Calcitonin inhibits osteoclast-mediated bone resorption. The parathyroid hormone stimulates calcitonin synthesis and also bone-calcium absorption and renal-calcium conservation. Salmon calcitonin is approved only for postmenopausal women who cannot tolerate estrogen, or for whom estrogen is not an option [56]. Now-a-days, Salmon calcitonin is also being made synthetically. It is similar to Salmon calcitonin and offers an economical way to create large quantities of the product [57].

4. 13. Squalamine

Squalamine is the first antimicrobial steroid isolated from an animal (fish). It is an aminosterol compound (molecular formula C34 H65 N3 O5 S) is found in a small- to medium-size dogfish shark (*Squalus acanthias*), which the body readily uses to carry out its normal anti-angiogenesis function. The compound is a potent antibacterial and has shown efficacy in treating human cancers and an eye condition known as macular degeneration, which causes blindness. New research shows it can also kill many human liver viruses. Its safety profile is well established, meaning it could rapidly be tested as a new class of medications for the treatment of various viruses, such as hepatitis, dengue or yellow fever [58]. Squalamine also contains many other factors which support the immune system.

4.14. Squalene and squalane

Some deep-sea sharks mainly *Centrophorus* spp. found at a depth of 300–3000m in the Pacific, North Atlantic, and Indian Ocean contain about 85–90% unsaponifiable matter, which is essentially the hydrocarbon, squalene (C30H50, 2,6,10,15,19,23-hexamethyl, 2,6,10,14,18,22-tetracosahexaene). Squalane is a saturated derivative of squalene. Squalene has remarkable antioxidant activity. In addition, this compound has been reported to possess antilipidemic and membrane-stabilizing properties. Supplementation of squalene also exerted membrane-stabilizing action against induced myocardial infarction by maintaining the activities of membrane-bound ATPases in heart tissues and the mineral status (Na, K, and Ca) in plasma and heart tissues. It was suggested that the cardio protective effect of squalene might be ascribable to its antioxidant action and membrane-stabilizing properties [59]. Squalene is a compound that captures hydrogen atoms from any source available to it. Therefore, Squalene may be the greatest oxygen enhancer existing in nature. Several studies exhibited results that prove certain bioactivities for squalene and squalane [60]. Squalene improves the health of skin EPA and DHA influenced prostaglandin balance. Squalene has also been found to be a natural inhibitor of an enzyme which helps to activate the ras oncogene which has been linked as the culprit in severe health problems.

4.15. Cardioprotective effects

Cardioprotection has been in the research focus for many years from many localities. Different pharmacological and non-pharmacological strategies have been proposed to decrease myocardial damage e.g. during ischemia reperfusion injury and cardio toxicity [61]. Several studies have shown beneficial cardiovascular effects of fish and its derivatives. The antioxidants are now much focused in order to know whether these antioxidants can prevent myocardial damage. A well known example for such a clinical application in the field of cardiovascular medicine is the fish derived long chain N-3 polyunsaturated fatty acids [62, 63]. There is also evidence that aqueous fish derived substances such as taurine, have cardioprotective effects. Taurine is generally found in high levels in seafood. It is involved in radical scavenging membrane regulation, osmoregulation and regulation of calcium homeostasis [64]. In animal models and in human trials the settings of CHF, taurine was found to have beneficial effects on cardiac function and morphology [65].

4.16. Astaxanthin as a potential cancer preventive

Salmon, the principal dietary source of astaxanthin, is an important component traditional diets of Eskimos and certain coastal tribes in North America. These groups have shown unusually low prevalence of Cancer [66-68]. This low cancer incidence has been attributed to the high levels in salmon of certain fatty acids, notably eicosapentaenoic acid (EPA) [69], yet it is possible that astaxanthin has played a role in cancer chemoprevention among these people as well. Regardless, the existing data on the potential for astaxanthin to directly prevent cancer is limited to *in vitro* cell culture studies and *in vivo* studies with rodent models.

4.17. Syngnathusin as an antitumor activities

Discovery and development of new antitumor agents from marine fish are attracting an increasing interest. A novel antitumor protein Syngnathusin from the whole body of *Syngnathus acus*, a precious marine fish traditionally used for tumors. Syngnathusin was comprised of 16 kinds of amino acids, mainly acidic amino acids. Its molecular weight was 67.3 kDa and its isoelectric point is 4.57. The N-terminal amino acid sequence of Syngnathusin was determined to be Lys-Arg-Asp-Leu-Gly-Phe-Val-Asp-Glu-Ile-Ser-Ala-His-Tyr. Syngnathusin could significantly inhibit the growth of A549 and CCRF-CEM cells. Flow cytometry, Morphologic assessment and Comet assay revealed that Syngnathusin could induce apoptosis in A549 and CCRF-CEM cells and strongly cooperated with MTX. Syngnathusin could inhibit the growth of S180 tumor transplanted in mice. Syngnathusin may be developed as a novel, selective and effective antineoplastic agent [70].

DISCUSSION

Staple foods are needed in large quantities because they supply the major part of the protein and other nutrients in the diet. So there is a need for both more food and special foods of better quality. Fish is leaner than meat, that is lower fat, and contains amino acids and minerals that are vital to the body. The importance of protein in human nutrition, and fish as a source of animal protein in maintenance of health has been known from time immemorial. It is also believed that, as people become increasingly aware of the association between diet and good health, the consumption of fishery products will most likely increase [71]. Fish have often been called the poor man's source of animal protein. Because it has a protein quality equal to that of meat, eggs, and milk, it has an important role to play in the diets of many populations. Supplementary foods that provide complementary protein and micronutrients are needed in relatively smaller quantities, but without them, the staple diet becomes qualitatively inadequate, particularly for vulnerable groups. This is where FPC could serve a useful purpose. The systematic use of fish concentrate has long proven advantageous in animal husbandry, and there is growing recognition of its potential for improving human nutrition and health. Recent studies have shown that fish-derived bioactive peptides play a vital role in human health and nutrition, and they can be a part of the human diet for several years. Adequate dietary intake of fish, which leads to hydrolytic release of these peptides, could therefore be therapeutically useful. More studies should be conducted to further explore the physiological effects of these peptides in humans. To enable this widespread use, it will be important to have convenient methods for the extraction, purification and identification of these bioactive peptides [72]. All aspects, including chemical composition, biotechnology, extraction, bioactivity, and toxicity should be considered. Fish-derived bioactive peptides with antioxidative properties may have great potential for use as nutraceuticals and pharmaceuticals and they may be a better substitute for synthetic antioxidants [73]. In addition, antimicrobial peptides from fish will provide a new source for the development of measurement novel antimicrobial drugs in the future. It is important to discover new antimicrobial substances because of the rise of pathogenic bacteria that are resistant to conventional antibiotics. These antimicrobial peptides can serve as vaccines in the future to inactive specific pathogens. They can also be used in food preservatives, and supplements. Marine fish are a rich and varied source of pharmacologically active natural products and nutraceuticals. A number of marine fish species have been identified with potential nutraceutical and therapeutics values [74]. Based on the evidence demonstrating their beneficial health effects, fish-derived bioactive peptides have the antioxidative and antimicrobial potential to be used as active ingredients in functional foods, food supplements and in the pharmaceutical industry [75].

CONCLUSIONS

Fish have obvious nutritional advantages over products such as fruits and vegetables or even other non-vegetarian diets. There is anywhere from 15gm to 30gm of protein in fish depending on the type of fish and how it is cooked. Modern technology has made it easy to explore the therapeutic importance of fish-based diet. From an economic and resource point of view it is important to note that there is sufficient raw material in the sea for the production of a new product like FPC in addition to, and not at the expense of, the present catch and production methods. Marine nutraceuticals are both a coherent and attractive option for the food industry as there are a multitude of functional food ingredients that can be derived from marine sources. Consequently, ongoing efforts should be made into the research and development of marine functional foods with prospect that, in the future, their consumption could lead to a reduction in the prevalence and severity of chronic diseases. Despite the vast possibilities for use of marine bioactives in food, more multidisciplinary research is needed. Further research should go in this direction in order to show new preventive and potential therapeutic strategies against several inflammatory chronic diseases [76-78]. Marine bioactives appear to fit the criteria for development as functional food ingredients. Firstly, they are widely available, with a guaranteed supply. Secondly, marine bioactives are naturally occurring compounds, and their isolation/extraction is relatively cost effective. Lastly, and probably most importantly, they are functional, their biological activities affect the pathogenesis of several diseases.

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