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Review Article

Biotechnology Section

Marine-Derived Bioactive Peptides with Pharmacological Activities- A Review

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ABSTRACT

Some nutritional factors are related to chronic disease. In response to increased concern regarding nutrition and health, the functional and nutraceuticals food markets have been developed. During food digestion, proteins are hydrolyzed and a wide range of peptides are formed. Some of these peptides have special structures which permit them to confer particular biological functions. Marine animals which involve more than half of the world biological varieties are a wide source of bioactive proteins and peptides. Marine derived peptides show various physiologic functions such as anti-oxidant, antimicrobial, anti-cancer, Angiotensin-1-Converting Enzyme (ACE) glucosidase and α-amylase inhibitory effects in vitro. Before application of marine bioactive peptides as nutraceuticals or functional food ingredients, their efficacy should be approved through pre-clinical animal and then clinical studies. The aim of this study was to review the studies conducted on the pharmacological effect of marine bioactive peptides in animal models and humans.

Keywords: Chronic disease, Pharmaceutical effect, Therapeutic properties

INTRODUCTION

Recent studies have shown a relation between nutritional factors and prevalence of some chronic disease [1]. In response to increased concern regarding nutrition and health, the functional food markets have been developed. The functional foods are those which provide body nutritional needs and also have health properties by regulating one or more physiological functions [2]. The world trade of functional foods has increased 6 percent in 5 recent years, and it is estimated to reach up to 54 billion dollars [3].

Marine animals that comprise about half of the world's biodiversity provided a wide spectrum of bioactive compounds which can be used in the production of functional foods [4]. Marine biologically active compounds include bioactive peptides, oligosaccharides, omega fatty acids, enzymes, minerals, pigments and bio-polymers [5].

Proteins are of most prominent nutritional compounds and excellent source of all essential amino acids. They are responsible for building, maintaining and repairing of body tissue and are one of the main energy sources. In addition, proteins in food affect sensory (texture, colour, taste and odour) and physico-chemical (solubility, viscosity, gel formation and emulsifying) [2]. Furthermore, some of proteins in nutritional regimens have biologic properties and improve the health of consumers. In this regard, it has been reported that fish protein can lower blood pressure and lipid and therefore decrease the risk of atherosclerosis and heart disease [3].

During food digestion, proteins are hydrolyzed and a wide range of peptides are formed. Some of these peptides have special structures which permit them to confer particular biological functions. These peptides have 2-20 amino acids and are released during hydrolysis process [6]. The released form of these peptides exhibits various physiologic functions such as immune stimulatory [7], anti-cancer [8], antimicrobial [9], anti-oxidant [10] and blood pressure, glucose and lipid lowering [6] activities due to their bioactive features.

Bioactive peptides are proteins synthesized in the cell in the form of large prepropeptides which are then cleaved and modified to give active products. They are obtained mainly from herbal and animal sources. Animal sources of bioactive peptides include milk, egg, red meat and marine animals [2]. Marine animals which involve more than half of the world biodiversity are a wide source of bioactive proteins and peptides [11]. There are increasing evidences that numerous peptides and protein hydrolysates derived from marine animals including fish, mollusks, crustaceans and fishery wastes (substandard meat, head, viscera, skin, fins and skeletons) can improve human health and prevent chronic diseases [2].

In general, bioactive peptides are obtained from whole protein molecules through enzymatic hydrolysis and fermentation. Digestion of protein by proteolytic enzymes and microbes during fermentation may increase their nutritional and pharmaceutical function [12]. Enzymatic hydrolysis is one of the most common methods used for the production of bioactive peptides. Enzymatic hydrolysis is carried out by employing autolytic process or commercial protease [13]. Various commercial proteases from plants, animals and microbial sources such as trypsin, chymotrypsin, pepsin, alcalase, papain, pronase and collagenase are used for the production of bioactive peptides. In addition, autolysis process by digestive or autolytic enzymes of animal can also be used for the production of bioactive compounds [14].

Pharmacologic effects of marine bioactive peptides in animal/and human models:

Until today, numerous studies have assessed the therapeutic properties of marine bioactive peptides in vitro and few studies have been performed over animal model or human [2]. The aim of the present study was an overview on the results of previous studies regarding therapeutic effects of marine bioactive peptides.

Hypotensive, hypolipidemic, hypocholesterolemic and anti-diabetic effects:

High blood pressure affects approximately 25% of adults today and is estimated to progress to 29% by 2025, a population of

1.56 billion [15]. The high blood pressure is associated with some cardiovascular diseases such as atherosclerosis, myocardial infarction and stroke. The ACE plays a critical role in the regulation of hypertension. The synthetic inhibitors of ACE enzyme can lead to different side effects [16]. A number of clinical trials have previously reported that consumption of some proteins in diet can lower blood pressure [2]. The effects of ACE inhibition by some marine peptides have been shown in vitro and those with the most level of inhibitory properties have been isolated and sequenced by chromatography methods [14,17,18]. The effects of purified peptides were also investigated in several studies. For example a single oral administration (10mg/kg of body weight) of the purified peptides isolated from fermented blue mussel [14], yellow fin sole frame [17] and izumi shrimp muscle [19] have been reported to reduce systolic blood pressure in spontaneously hypertensive rats. Long-term oral administration of jellyfish collagen peptides has also shown antihypertensive activity in renovascular hypertensive rats [20].

Hyperlipidemia and hypercholesterolemia have an important role in the occurrence of atherosclerosis, coronary artery disease, ischemic heart disease and peripheral vascular disease [21]. Epidemiological studies show that Greenland Eskimos and Japanese fishermen who eat more fish appear to have a lower rate of heart disease [22]. Possible roles of fish protein in reducing the risk of cardiovascular diseases might be related to their hypolipidemic and hypocholesterolemic activities [5]. The evidence has suggested that protein hydrolysate derived from soybean [23] and fish [24] show better anti-hyperlipidemic effect than non-hydrolyzed proteins. Hypolipidemic and hypocholesterolemic activity of protein hydrolysate derived from muscle of bogue [24], sardine [25], Alaska pollock [26,27] and zebra blenny [28] have been shown in rat fed on high cholesterol and high fat diet. They reduce atherosclerotic development through several mechanisms including reduction of serum lipid such as Total cholesterol, Triglycerides and low-density lipoprotein (TG, TC, and LDL), reduction of serum Malondialdheyde (MDA), and increase activities of antioxidant enzymes.

The prevalence of diabetes is increasing promptly worldwide and more than 194 million people have been afflicted. It has been estimated that the number of patients reach to 335 million in 2025. Of diabetes types, the type 2 diabetes is highly prevalent and involves 90% of cases [29]. Although some drugs, dietary patterns and exercise program have improved hyperglycaemia due to diabetes, these programs cannot efficiently inhibit and prevent its complications. Therefore, discovery and development of new drugs has crucial importance [30]. As exhibited in [Table/Fig-1] [14,17,19,20,24-28,30-33], some peptides and hydrolysis proteins from marine sources are also able to heal hyperglycaemia, oxidative stress and liver and kidney damage induced by diabetes in animal models and human. It is reported that the administration of protein hydrolysates from zebra blenny muscle has hypoglycemic and hypolipidemic effects in alloxan-induced diabetic rats. It also shows potent hepatoprotective against alloxan induced hepatic damage [30]. Protein hydrolysates obtained from goby fish muscles have also been shown to display ameliorating effects on hyperglycaemia, oxidative stress and nephrotoxicity in rats fed on high-fat-high-fructose diet [31]. Clinical research shows that taking oral MCPs provides protection against hyperglycaemia, hypertension and dyslipidemia in type 2 diabetic patients [32,33]. These effects might be related to the regulation of the level of molecules involved in diabetic and hypertensive pathogenesis such as hs-CRP, nitric oxide, bradykinin, PGI2 and adiponectin [32,33].

Skin protection and wound healing:

The skin is the largest organ of the body which protects it from damaging agents. The collagen involves 30% of total body and 70% of skin proteins. There are more than 20 recognized collagen types which classified in three main groups. Type 1 collagen which is the predominant collagen in the body, has an important role in maintenance of skin integrity [34]. Skin ageing is accompanied by significant decrease in type 1 collagen [35]. Previous studies have shown that consumption of collagen peptides have positive effects on hair thickening, improvement of nail disorders, increasing size of collagen fibrils, increasing density of fibroblasts and formation of collagen fibrils in the dermis [34]. Marine by products contain 30% collagen which is a potential source for production of collagen peptides [36]. Skin protection and wound healing activities of collagen peptides derived from marine resources are exhibited in [Table/Fig-2] [36-38]. Collagen peptides prepared from chum salmon skin have been reported to exhibit wound healing [36] and skin protection properties [37]. In a single-blind case-control clinical study, 2-month oral intake of marine collagen peptides remarkably improved skin elasticity, sebum production and dermal ultrasonic markers in healthy volunteers [38].

Immunomodulatory effects:

Uncontrolled and inappropriate use of antibiotics has resulted in the emergence of new complicated and opportunistic pathogens resistant to commonly used antibiotics. So, researchers are interested in controlling these agents not only by discovering new antimicrobials and antibiotic therapy but also by discovering new antimicrobial compounds having immunomodulatory effect [39].

It has been reported that peptides from enzymatic hydrolysis of herbal (fermented rice) [39] and animal (casein in milk and egg albumin) [40,41] proteins have immunomodulatory effects. Marine animal are another important source of bioactive peptides with numerous immunomodulatory activities. Several studies regarding the immunomodulatory effects of marine bioactive peptides in animal models and human are shown in [Table/Fig-3] [3,7,42,43]. Oyster hydrolysate was observed to inhibit the growth of transplantable sarcoma-S180 in mice by approximately 40%. Also, the immunomodulatory effects in S180-bearing mice were reported. Oyster hydrolysate is supposed to show immunomodulatory effects through interaction with Natural Killer (NK) cells, lymphocyte and macrophage [7]. Oligo-peptides produced by enzymatic hydrolysis of chum salmon have been shown to have immune-stimulatory properties on UV-induced immune suppression in mice. Mice fed with oligo-peptides showed significant increase in lymphocyte proliferation, number of plaque-forming cells, activity of natural killer, Th1 and CD4 cells [42]. Commercial peptide derived from shark protein has also been shown to stimulate immune response in healthy volunteers [3].

Neuroprotective and analgesic effects:

The decreased function of brain due to human ageing can lead to cognitive disorders such as memory impairment and amnesia. In 21st century, the global population goes toward ageing which is accompanied by related diseases such as Alzheimer's and Parkinson [44]. Oxidative stress is an important risk factor in the development of age-related memory and learning deficits. High generation of reactive oxygen species in conjunction with the weakened antioxidant defense system can lead to neuronal damage and eventually neurological disorders [45]. Today, various antioxidants are widely in use to prevent and treat some of these conditions [44-46].

Source	Peptide concentration and treatment period	Mechanism of effect	Ref
Mytilus edulis	Purified peptide isolated from fermented mussel at 10mg/kg	Reduction of blood pressure in the spontaneously hypertensive rats	[14]
Limanda aspera	Purified peptide isolated from frame protein hydrolysate at 10mg/kg	Reduction of blood pressure in the spontaneously hypertensive rats	[17]
Plesionika izumiae	Purified peptide isolated from izumi shrimp muscle	Reduction of blood pressure in the stroke-prone spontaneously hypertensive rats	[19]
Rhopilema esculentum L	25 and 100 mg/kg of hydrolysate protein for 20 days	Reduction of systolic and diastolic blood pressure, reduction of angiotensin II in the kidney of renovascular hypertensive rats	[20]
Boops boops	Diet containing 10% muscle protein hydrolysates	Reduction of serum level of TC, TG, LDL, HDL, ALT[1], ALP[2] and AST[3], reduction of liver MDA and increases activity of liver antioxidant enzymes in rats fed a high cholesterol diet	[24]
Sardinella aurita Sardina pilchardus	Protein hydrolysates at 300 mg/kg for 14 days by gavage	Reduction of serum TC, LDL and HDL, reduction of MDA in RBC, heart and aorta, increases activities of antioxidant enzymes in heart and RBC of rats fed a cholesterol-rich diet	[25]
Theragra chalcogramma	Diet containing 10% muscle protein hydrolysates	Increases excretion of neutral and acidic sterols, reduction of serum cholesterol in the high-fat diet–fed rats.	[26]
Theragra chalcogramma	Diet containing 10% muscle protein hydrolysates	Reduction of TC, TG and LDL and increase of fecal excretion of bile acids and cholesterol in rats fed high-cholesterol diets	[27]
Salaria basilisca	Protein hydrolysates 300 mg/kg by gavage for 4 weeks	Reduction of TC, TG, LDL, MDA, uric acid, urea, creatinine, ALP, AST and ALT level of serum, inhibition of liver and kidney histopathological changes, increases activity of antioxidant enzymes in cholesterol-fed rats	[28]
Salaria basilisca	Protein hydrolysates at 300 mg/kg by gavage for 4 weeks	Reduction of serum and intestines amylase activity, reduction of serum glucose, HbA1c, TC, TG and LDL, strong protective effects on markers of heart attack by reducing myocardial enzymes, reduction of serum bilirubin, ALT, ALP and AST in alloxan-induced diabetic rats	[30]
Zosterisessor ophiocephalus	Protein hydrolysates 400mg/kg for 30 days by gavage in rat	Reduction of serum glucose, liver glycogen, alpha-amylase activity and serum MDA, increases activities of liver antioxidant enzymes, inhibition of kidney histopathological change in rats fed with high-fat-high-fructose diets	[31]
Marine collagen peptide	MPC for three months before bedtime	Reduction of free fatty acid, hs-CRP, resistin, prostacyclin, cytochrome P450, leptin and nitric oxide and increases of bradykinin in type 2 diabetic patients with/without hypertension	[32]
Marine collagen peptides	MCP at 13 grams per day for three months	Reduction of fasting blood glucose, fasting blood insulin, HbA1c, TG, TC, LDL and increases of serum HDL. Increases of insulin sensitivity, reduction of hs-CRP and nitric oxide, increases of bradykinin, PGI2 and adiponectin in patients with type 2 diabetes mellitus	[33]

[Table/Fig-1]: Studies depicting the hypotensive, hypolipidemic, hypocholesterolemic and anti-diabetic effects of bioactive peptides.
[1] Alanine Aminotransferase (ALT)
[2] Alkaline Phosphatase (ALP)
[3] Aspartate Aminotransferase (AST)

Source	Peptide concentration and treatment period	Mechanism of Effect	Ref
Oncorhynchus keta	2 g/kg of skin collagen peptides for 20 days in rats	Increases of wound closure, tissue regeneration, angiogenesis and deposition of collagen	[36]
Oncorhynchus keta	Skin collagen peptides at 0.13, 0.38 and 1.15 g/kg for 20 days in Sprague Dawley rat	Increases of skin tensile strength, hydroxyproline concentration, formation of capillaries, fibroblasts and collagen fibers.	[37]
Marine collagen peptides	Collagen peptides (57 mg) for 2 months in healthy volunteers	Improvement of skin properties (elasticity and sebum production) and ultrasound markers (thick epidermis/dermis and acoustic density).	[38]

[Table/Fig-2]: Studies conducted on the skin protection and wound healing effects.

Source	Peptide concentration and treatment period	Mechanism of Effect	Ref
Commercial PeptiBal™	Commercial peptides at 300 mg/kg daily for 4 weeks in healthy volunteers	Immune modulation through increasing serum IgA	[3]
Crassostrea gigas	Oligopeptide at 0.25, 0.5 and 1 mg/kg by gavage in S180-bearing mice	Inhibition of Sarcoma 180 tumour by approximately 40%, increases coefficient of thymus and spleen weight, activity of natural killer cells, lymphocyte proliferation and macrophage phagocytosis rate	[7]
Oncorhynchus keta	Oligo-peptides at 0, 0.22, 0.45 and 1.35 g/kg by gavage for 4 weeks against radiation-induced immune suppression in mice	Increases of lymphocyte proliferation, number of plaque-forming cells, activity of natural killer, T helper and CD4+ T cells and production of cytokines by T helper[1] and T helper[2]	[42]
Commercial "Seacure"	Commercial peptides at 0.2, 0.25 and 0.3 mg/kg by gavage for 7 days in mice	Increases phagocytosis of peritoneal macrophages, IgA+ cells, IL-4[1], IL-6[2], IL-10[3], IFNγ[4] and TNFα[5]	[43]

[Table/Fig-3]: Studies conducted on the immunomodulatory effects.
[1]Interleukin 4
[2]Interleukin 6
[3]Interleukin 10
[4]Interferon gamma (IFNγ)
[5]Tumour necrosis factor (TNFα)

There are few and limited studies on the protective effects of marine bioactive peptides on memory and learning deficits [Table/Fig-4] [47-49]. Marine Collagen Peptide (MCP) isolated from chum salmon was shown to ameliorate age-related cognitive deficits in C57BL/6J mice [47]. It also reported to increase life span and inhibit development of spontaneous tumours in Sprague-Dawley rats [48]. The protective effects of MCP on age-related neurodegeneration are related to the inhibition of oxidative stress and apoptosis in neuronal cells. It also promotes expression of neurogenesis Brain-Derived Factor (BDNF) in the hippocampi of aged rats [47,48].

Anti-obesity and satiety enhancing effects:

In recent years, lifestyle modification has led to appearance of new health problems such as overweight and obesity. Overweight and obesity are known to increase the risk of several chronic diseases including coronary heart disease, type 2 diabetes mellitus, hypertension, stroke and some type of cancers [50].

Source	Peptide concentration and treatment period	Mechanism of Effect	Ref
Oncorhynchus keta	Diet containing collagen peptide at 0.22, 0.44 and 1.32% for three months in mice	Improvement of learning and memory, inhibition of oxidative stress and apoptosis in neuronal cells, increases expression of neurogenesis brain-derived factor (BDNF)	[47]
Cyprinus carpio	Diet containing collagen peptide at of 0, 2.25, 4.5 and 9 mg/kg in rats	Increase of life span and decrease of spontaneous tumour incidence. Increases activity of antioxidant enzymes. Reduction of serum MDA	[48]
Acanthina punctulata	Intrathecal injection of peptides conantokin-G and ω-conotoxin MVIIA in rats	Decreased response to pain	[49]

[Table/Fig-4]: Studies on the neuroprotective effects.

Source	Peptide concentration and treatment period	Mechanism of Effect	Ref
Pollachius pollachius	Diet containing saithe *(Pollachius pollachius)* protein hydrolysate at 230 g/kg for 26 days in rats	Increases plasma bile acids and expression of genes involved in fatty acid oxidation and energy production, decreases of liver lipids and visceral fat	[53]
Mustelusmustelus	Protein hydrolysate at 10 mg/ml by gavage for 3 weeks in rats	Reduction of weight and food intake through stimulating the release of CCK	[54]
Micromesistiuspoutassou	Protein hydrolysate at 50, 100 and 150 mg/g, 3 times a day for 8 days in rats	Increases secretion of cholecystokinin (CCK) and glucagon-like peptide-1 (1-GLP), reduction of food intake, increases weight loss	[55]
Micromesistiuspoutassou	Protein hydrolysate 1 g/kg twice a day in overweight women	Significant decrease in weight and food consumption	[56]

[Table/Fig-5]: Studies performed on the anti-obesity and anti-appetite effects.

Body weight is regulated by some endocrine hormones such as insulin and leptin. In addition, short messaging peptides, such as cholecystokinin, glucagon-like Ptyd -1 (GLP-1) and ghrelin are also involved in appetite and weight control [51]. Among various food compounds, proteins and their hydrolysate can stimulate the secretion of CCK and GLP-1 [52]. A summary of studies on the anti-obesity and anti-appetite effects of marine peptides are presented in [Table/Fig-5] [53-56]. The elevated plasma bile acids with saithe protein hydrolysate, rich in taurine and glycine, intake was observed in rats but soy protein or casein intake did not caused such effect. It is reported that conjugation of bile acids to taurine or glycine promotes their solubility and increases liver bile acids secretion. These muscle derived peptides were shown to reduce liver and visceral lipids and up regulate the expression of genes involved in fatty acid oxidation and energy production [53]. Low molecular weight peptides from smooth hound and blue whiting muscle protein have been shown to reduce food intake and appetite in rats [54,55]. These peptides were shown to stimulate the release of satiety hormones such as Cholecystokinin (CCK) and glucagon-like peptide-1 (1-GLP) from the gastrointestinal tract [54]. Protein hydrolysate derived from blue whiting muscle also shows weight loss benefits in overweight women [56].

DISCUSSION

Until now, therapeutic effects of marine bioactive peptides have been studied in vitro and in cell culture, but there are fewer studies in animal models [2]. The present study was an overview on therapeutic effects of bioactive peptides in animal models and human. As summarized in [Table/Fig-1-5], the positive effects of marine bioactive peptides in animal model include immune stimulation, blood pressure, lipids and glucose lowering, anti-obesity and satiety enhancing, skin protection and wound healing as well as memory and learning enhancing properties. In addition, the effects of marine bioactive peptides in protecting the liver against alcohol injury [57], development of long bone [58] and anti-oxidative stress [59] have been reported in animal models. According to tables, anti-obesity and satiating effects of protein hydrolysate from blue whiting muscle [32] and antihypertensive, antidiabetic and skin protection activities of marine collagen peptides [33,38] have been shown in human trials.

Before introducing bioactive peptides into market or their consumption as food components, there is a need to approve their therapeutic features in human studies and to take legal permits from the relevant authorities Food For Specified Health Uses (FOSHU), Food and Drug Administration (FDA), and European Food Safety Authority (EFSA) [13].

A number of peptides and proteins hydrolyzed derived from marine resources are sold with different brand names around the world. Some of these products have been shown to exhibit pharmacological activities in animal model and human. Human trials have shown that peptides in Valtyron® have antihypertensive effects in hypertensive subjects [18]. The immunomodulatory effects of two natural products such as PeptiBal™ [3] and Seacure [43] were also observed in healthy volunteers. Ziconotide is a natural peptide obtained from cone snail which shows analgesic activity in subjects with chronic pain [60]. Ziconotide and Valtyron® have recently been passed as safe by the EFSA and FDA [60].

Each year, both onboard and on-shore marine processing plants generate large amount of waste including substandard muscles, viscera, heads, skins, fins, frames and shell waste. Furthermore, large quantities of fish, molluscs and crustaceans are discarded due to small size or low consumer preference. It is estimated that about 64 million tons of low-value marine animals and by-products is discarded each year and most of them are used as fertilizer and animal feed [11]. This waste could be utilized as valuable sources for the production of bioactive peptides which lead to better exploitation of marine resources [2].

In general, substrate protein, type of enzymes and hydrolysis time and conditions (like temperature and pH) can affect structure and molecular weight of peptides and therefore their biological activities [13]. In order to produce peptides with certain molecular weight and specific activity, peptides are isolated and purified using ultrafiltration and chromatographic methods. The sequences of purified peptide are determined using mass spectrometry [59]. The sequenced peptides can be synthesized to evaluate their biological activities in animal models and human. Production of protein hydrolysis from marine animals or by-product is economically affordable and cost-effective, but production of peptides with specific sequences in commercial scale is limited due to high cost of peptides synthesis [13].

CONCLUSION

Marine bioactive peptides produced from different sources of protein through enzymatic hydrolysis or fermentation have been demonstrated to possess diverse physiological functions such as immune stimulation, blood pressure and lipids lowering, anti-diabetic, anti-obesity, skin protection and wound healing activities as well as memory and learning enhancing property in animal model or in human. Marine bioactive peptides seem to have a potential as a functional ingredient in food product or nutraceuticals to increase consumer health and wellbeing.

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