Review

Biological activities and potential health benefits of bioactive peptides derived from marine organisms

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ABSTRACT

Marine organisms have been recognized as rich sources of bioactive compounds with valuable nutraceutical and pharmaceutical potentials. Recently, marine bioactive peptides have gained much attention because of their numerous health beneficial effects. Notably, these peptides exhibit various biological activities such as antioxidant, anti-hypertensive, anti-human immunodeficiency virus, anti-proliferative, anticoagulant, calcium-binding, anti-obesity and anti-diabetic activities. This review mainly presents biological activities of peptides from marine organisms and emphasizing their potential applications in foods as well as pharmaceutical areas.

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1. Introduction

The world’s oceans, covering more than 70% of the earth’s surface, represent an enormous resource for the discovery of potential therapeutic agents. During the last decades, numerous novel compounds have been found from marine organisms with interesting pharmaceutical activities [1–4]. Therefore, marine organisms are believed to be a potential source to provide not only novel biologically active substances for the development of pharmaceuti...
2. Development of bioactive peptides derived from marine organisms

Components of proteins in marine foods are containing sequences of bioactive peptides, which could exert a physiological effect in the body. Especially, some of these bioactive peptides have been identified to possess nutraceutical potentials that are beneficial in human health promotion. Moreover, the possible roles of marine food-derived bioactive peptides in reducing the risk of diseases have been reported. Bioactive peptides usually contain about 3–40 amino acid residues, and their activities are based on amino acid composition and sequence. These short chains of amino acids are inactive within the sequence of the parent protein, but can be released during gastrointestinal digestion, food processing, or fermentation [10,11].

Bioactive peptides can be produced by in vitro enzymatic hydrolysis of different marine resources using appropriate proteolytic enzymes. Proteolytic enzymes from fish and aquatic invertebrates can be used for the hydrolysis process of marine products to develop bioactive peptides and applied in the food industry. The physicochemical conditions (temperature and pH) of the reaction media must be adjusted to optimize the activity of the enzyme used [12–14]. The crude proteinase was extracted from the pyloric caeca of tuna for the enzymatic hydrolysis of cod frame protein under optimal pH and temperature conditions of the respective enzymes to obtain maximum yield. Furthermore, the molecular weight of the bioactive peptides is one of the most important factors in releasing peptides with desired functional properties [15,16]. Therefore, a suitable method for the production of bioactive peptides with specific functional properties and desired molecular size characteristics is the use of an ultrafiltration membrane reactor system. This system has the main advantage that the molecular weight distribution of the desired functional peptide can be controlled by adoption of an appropriate ultrafiltration membrane. In order to obtain functionally active peptides, it is a suitable method to use a three enzymes system for sequential enzymatic digestion. Moreover, it is possible to obtain serial enzymatic digestions in a system using a multi-step recycling membrane reactor combined with ultrafiltration membrane system to separate marine-derived bioactive peptides [17,18]. This membrane bioreactor technology equipped with ultrafiltration membranes is recently emerging for the development of bioactive compounds and considered as a potential method to utilize marine proteins as a value added nutraceuticals with beneficial health effects.

3. Biological properties of marine bioactive peptides and potential health benefits

3.1. Antioxidant activity

Antioxidants may have a positive effect on human health since they can protect human body against deterioration by free radicals and reactive oxygen species (ROS), including singlet oxygen, hydrogen peroxide, superoxide anion, and hydroxyl radicals. ROS and free radicals attack macromolecules such as DNA, proteins and lipids, leading to many health disorders including inflammatory, aging, diabetes, neurodegenerative, cardiovascular and cancer diseases [19,20].

To retard peroxidation processes in food, many synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tert-butyldihydroquinone (TBHQ) and propyl gallate (PG) have been used. However, the use of these synthetic antioxidants must be strictly controlled due to their potential health hazards. Hence, search for natural antioxidants as safe alternatives to synthetic products is important in the food industry. Recently, the use of natural antioxidants available in food and other biological substances has attracted significant interest due to their presumed safety, nutritional and therapeutic values [21–23]. A number of studies have shown that peptides derived from various marine protein hydrolysates such as fish [13], blue mussel [24], conger eel [25], microalgae [26] and squid [27] act as potential antioxidants (Table 1). The antioxidant activity of bioactive peptides derived from marine has been determined by different in vitro methods, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), carbon-centered, hydroxyl and superoxide anion radical scavenging activities which have been detected by electron spin resonance (ESR) spectroscopy method as well as intracellular free radical scavenging assays. The beneficial effects of antioxidant marine bioactive peptides are well known in scavenging ROS and free radicals or in preventing oxidative damage by interrupting the radical chain reaction of oxidation [36]. Oxidation in foods affects lipids, proteins and carbohydrates. However, lipid oxidation is the main cause of deterioration of food quality, leading to rancidity and shortening of shelf-life. Oxidation of proteins in foods is influenced by lipid oxidation, where lipid oxidation products react with proteins causing their oxidation. Carbohydrates are also susceptible to oxidation, but they are less sensitive than lipids and proteins [37]. Bioactive peptide from jumbo squid inhibited lipid peroxidation in the linoleic acid model system and its activity was much higher than α-tocopherol, and was close to highly active synthetic antioxidant, BHT [28]. Moreover, the bioactive antioxidant peptide from oyster (Crassostrea gigas) exhibited higher protective activity against polysaturated fatty acid peroxidation than natural antioxidant, α-tocopherol [30].

The antioxidant activity is suggested to be due to the specific scavenging of oxygen containing compounds, or metal-chelating ability, scavenging of radicals formed during peroxidation. In addition, peptides isolated from marine fish proteins have greater antioxidant properties than α-tocopherol in different oxidative systems [35]. Antioxidant activities of bioactive peptides are mainly due to the presence of hydrophobic amino acids, some aromatic amino acids and histidine. Gelatin peptides are rich in hydrophobic amino acids, and the abundance of these amino acids favors a higher emulsifying ability. Hence, marine gelatin peptides possess higher antioxidant effects than peptides derived from other proteins because of the high percentage of glycine and proline [28]. Therefore, antioxidant bioactive peptides derived from marine may have great potential use in pharmaceuticals, nutraceuticals and as a substitute for synthetic antioxidants. For example, Shahidi et al. [38] clearly demonstrated that capelin fish protein hydrolysate which added to minced pork muscle at a level of 0.5–3.0% reduced the formation of secondary oxidation products including thiobarbituric acid reactive substances (TBARS) in the product by 17.7–60.4.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Antioxidant peptides derived from marine organisms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Amino acid sequence</td>
</tr>
<tr>
<td>Conger eel</td>
<td>LGNLDGDVRN</td>
</tr>
<tr>
<td>Microalgae</td>
<td>VECCVPRQGF</td>
</tr>
<tr>
<td>Squid</td>
<td>NADFCLNGLEGLA</td>
</tr>
<tr>
<td></td>
<td>NGLCLK</td>
</tr>
<tr>
<td></td>
<td>FDSCPGVYL</td>
</tr>
<tr>
<td></td>
<td>NGCGLAGPGGER</td>
</tr>
<tr>
<td>Hoki</td>
<td>ESTVPERTHAPCODFPN</td>
</tr>
<tr>
<td>Oyster</td>
<td>LKQELEDLQKE</td>
</tr>
<tr>
<td>Blue mussel</td>
<td>HFCGQPH</td>
</tr>
<tr>
<td>Tuna</td>
<td>VKAGFAWNTANQLS</td>
</tr>
<tr>
<td>Rotifer</td>
<td>LLPGCLTNAHA</td>
</tr>
<tr>
<td></td>
<td>DLGLGPLCAH</td>
</tr>
<tr>
<td>Prawn</td>
<td>IJK, FIK, and FK</td>
</tr>
<tr>
<td>Yellowfin sole</td>
<td>RPDFDLEPPY</td>
</tr>
</tbody>
</table>
However, the bitter taste of protein hydrolysates prevents the use of bioactive peptides as food additives [39] and the bioactivity may be reduced through molecular alteration during food processing or interaction with other food ingredients [40]. As a treatment to this bitterness, Shahidi et al. [38] treated fish protein hydrolysate with activated carbon, which removed bitter peptides. Also, the plastein reaction which can occur when a protein hydrolysate is incubated with a protease is able to debitter protein hydrolysates [41]. Incorporation of a fish protein hydrolysate preparation made by autolysis of arrowtooth flounder protein into a coating of salmon filets slowed down the lipid oxidation process. Furthermore, a brine solution containing salmon fish protein hydrolysate injected into smoked salmon fish filets was shown to reduce lipid oxidation measured as TBARS during 8 months of frozen storage (−18 °C) and 6 weeks of cold storage (4 °C) [42]. The challenge for food technologists will be to develop functional foods and nutraceuticals without the undesired side effects of the added peptides.

### 3.2. Anti-hypertensive activity

High blood pressure is increasingly prevalent in developed countries and one of the major independent risk factors for myocardial infarction, congestive heart failure, arteriosclerosis, stroke, and end stage renal disease [43]. Angiotensin-I-converting enzyme (ACE) plays a critical physiological role in regulation of blood pressure by converting angiotensin-I to angiotensin-II, a potent vasconstrictor. Therefore, the inhibition of ACE activity is a major target in the prevention of hypertension [44]. Currently, many natural ACE inhibitory peptides have been isolated from different food proteins such as cod frame, pollack skin, sea bream scales, yellow sole frame, tuna frame and clam, krill, mussel, oyster, and shrimp [45] (Table 2). Hence, a great interest has been developed nowadays to obtain bioactive peptides, which could be applied in the prevention of hypertension and in the initial treatment of mildly hypertensive individuals [63].

The competitiveness against ACE activity of different anti-hypertensive peptides has been determined kinetically using Lineweaver–Burk plots [60]. Generally, the mechanism of action of anti-hypertensive peptides is different from that of synthetic drugs. The synthetic drugs basically indiscriminately block ACE by interfering with its action while ACE inhibitory peptides interact much differently by competing with ACE. ACE converts angiotensin-I to angiotensin-II by cleaving off a small peptide. Synthetic drugs work by directly blocking the action of ACE. ACE actually reacts with the anti-hypertensive peptides instead of attacking angiotensin-I. Anti-hypertensive peptides relax the arterial walls and reduce fluid volume by inhibiting the formation of angiotensin-II. Therefore, anti-hypertensive peptides actually improve heart function and increase blood and oxygen flow to the heart, liver and kidneys [64]. Many studies have shown that tryptophan, tyrosine, phenylalanine or proline at the C-terminal, and branched-chain alphatic amino acids at the N-terminal were suitable for a peptide binding to ACE as a competitive inhibitor [65].

In addition, a non-competitive mechanism has also been observed in some peptides [49] which were suggested to combine with an enzyme molecule to produce a dead-end complex, regardless of whether a substrate molecule is bound or not. For example, YLYEIR [66] and LIY [67] have been found to act as non-competitive inhibitors. The hydrophobicity of the N-terminus, which is one of the common features of ACE inhibitory peptides, may contribute to the inhibitory activity [68]. ACE inhibitory peptides are generally short chain peptides, often carrying polar amino acid residues such as proline. Furthermore, structure–activity relationships among various peptide inhibitors of ACE indicate that binding to ACE is strongly influenced by the C-terminal tripeptide sequence of the substrate, and it is suggested that peptides, which contain hydrophobic amino acids at these positions, are potent inhibitors [16].

Numerous in vivo studies of anti-hypertensive peptides derived from marine in spontaneously hypertensive rats (SHR) have shown potent ACE inhibitory activity [60]. In general, the reduction in systolic blood pressure (SBP) following oral administration (10 mg/kg of body weight) of peptides was on average 25 mmHg compared to controls [62,69,70]. This anti-hypertensive activity was similar with captopril, a commercial anti-hypertensive drug. Protein hydrolysates derived from oyster proteins and sea bream scale collagen have also exhibited anti-hypertensive activity in SHR [53,71]. However, variations in sample type, the dosage and duration of administration make it difficult to compare these hydrolysates in terms of SBP reduction.

### 3.3. Anti-human immunodeficiency virus activity (anti-HIV)

Numerous studies have been reported that marine bioactive peptides can be used as anti-HIV components in functional foods or nutraceuticals and pharmaceuticals due to their therapeutic potential in the treatment or prevention of infectious diseases (Table 3).

Lee and Maruyama [72] searched for HIV-1 protease-inhibiting substances from oyster C. gigas. Two peptides inhibiting HIV-1 protease, LLEYSL and LLEYSL, were isolated from the hydrolysate of...
of oyster proteins prepared with thermolysin. LLEYSI and LLEYSI exhibited strong inhibition of HIV-1 protease at IC50 values (50% inhibitory concentration) of 20 and 15 nM, respectively, and behaved as competitive inhibitors for HIV-1 protease with Ki values of 13 and 10 nM, respectively. Lee and Maruyama [72] have searched that the length of amino acid sequence and the presence of C-, N-terminal hydrophobic amino acids in these peptides are important for their inhibitory activity.

Besides, sponges have been traditionally known as a source of novel bioactive peptides. The novel structural features and diverse biological activities of these peptide metabolites have generated considerable interest. Mirabamides from the marine sponge *Siliquaria* *sp. mirabilis* have been shown to potently inhibit HIV-1 fusion. Among mirabamides, mirabamide A was found to powerfully inhibit HIV-1 in neutralization and fusion assays with respective IC50 values of 40 and 140 nM, while mirabamides C and D were shown at less effects (IC50 values between 140 nM and 1.3 μM for mirabamide C and 190 nM and 3.9 μM for mirabamide D). Furthermore, mirabamides inhibited HIV-1 at the level of membrane fusion, presumably through interactions with HIV-1 envelope glycoproteins [73]. In addition, celebesides A and theopapuamide B have been isolated from sponges of the same previously mentioned *S. mirabilis*. Celebesides A is cyclic depsipeptide incorporating a polyketide moiety and five amino acid residues, among which are the unusual amino acids phosphoserine and 3-carbamoyl threonine. Theopapuamide B is a undecapeptide comprising two previously unreported amino acids, 3-acetamido-2-aminopropanoic acid and 4-amino-2,3-dihydroxy-5-methylhexanoic acid. Theopapuamide B was active in the neutralization assay with an IC50 value of 0.8 μg/ml while celebesides A displayed an inhibition of HIV-1 entry with an IC50 value of 1.9 μg/ml. In addition, the anti-HIV activity of celebesides A correlates the presence of phosphoserine residue but absent in the inactive theopapuamide [74]. However, this hypothesis was ruled out by the evidence given in the study of Zampella et al. [75]. A novel anti-HIV cyclodepsipeptide from the marine sponge *Homophyma sp.* is homophymine A containing an amide-linked 3-hydroxy-2,4,6-trimethylxanoic acid moiety. 11 amino acid residues and four unusual amino acid residues: (2S,3S,4R)-3,4-diMe-Gln, (2R,3R,4S)-4-amino-2,3-dihydroxy-1,7-heptanoic acid, t-ThrOMe, and (2R,3S,4R)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid. Obviously, homophymine A lacks β-methoxytyrosine residue replaced by an O-methyl threonine residue, however, homophymine A was reported to potently exhibited cytoprotective activity against HIV-1 infection with an IC50 value of 75 nM. The anti-viral activity found in homophymine A ruled out the hypothesis that β-methoxytyrosine is essential for anti-viral activity.

In a similar trend, depsipeptides isolated from a number of marine sponges have been identified to be active as HIV inhibitors. Neamphamide A, a novel HIV-inhibitory depsipeptide obtained from marine sponge *Neamphius huxleyi*, exhibited a potent cytoprotective activity against HIV-1 infection with an EC50 (50% effective concentration) of 28 nM [76]. Similar to neamphamide A, callipeltin A, a novel anti-viral and anti-fungal cyclodepsipeptide from sponge of the genus *Callipelta*, exhibited the inhibition of cytopathic effects on CEM4 lymphocytic cell lines infected with HIV-1 at an EC50 value of 0.01 μg/ml [77]. The general structure of callipeltin A with the N-terminus blocked and the C-terminus lactonized with a threonine residue is similar to a family of potent anti-tumor and anti-viral, didemmins, which possesses anti-HIV activity.

On the other hand, the novel cyclic depsipeptides papuamides A and B have been isolated from sponges *Theonella mirabilis* and *Theonella swinhoei* [78]. They contain not only unusual amino acids including β-methoxytyrosine, 3-methoxyalanine, 3,4-dimethylglutamine, 2-amino-2-butoic acid and or 2,3-diaminobutanoic acid residues but also the first peptides derived from marine reported to contain homoproline and 3-hydroxyxyleucine residues. They also contain a previously undescribed 2,3-dihydroxy-2,6,8-trimethyldeca- (4Z,6E)-dieneoic acid moiety N-linked to a terminal glycine residue. They were reported to block the infection of human T-lymphoblastoid cells by HIV-1 sub(RF) in vitro with an EC50 of approximately 4 ng/ml. The papuamides A can block at the early stage of the viral life cycle, but not in HIV-1 envelope glycoprotein specific [3,79]. Papuamide B also inhibits viral entry via interaction of this peptide to phospholipid present on the viral membrane at a concentration of 710 nM [80]. Another anti-HIV candidate is the microinosamidase, a new cyclic depsipetide incorporating 13 amino acid residues isolated from the sponge *Sidonops microspinosus*. This peptide is the first naturally occurring peptide to contain a β-hydroxy-p-bromophenylalanine residue. Microinosamidase inhibited the cytopathic effect of HIV-1 infection in an XTT-based in vitro assay with an EC50 value of approximately 0.2 μg/ml [81]. Accordingly, sponges-derived peptides are indicated as promising candidates for the design of novel strong inhibitors of viral infection.

### 3.4. Other biological activities

Besides, marine peptides have also been found to exhibit anticancer, anti-coagulant, anti-diabetic, anti-obesity, and calcium-binding activities (Table 4). According to the recent studies, the anti-cancer activity of marine peptides has been evidenced due to induction of apoptosis and inhibition of cell proliferation in vitro. These peptides were obtained from anchovy sauce [82,83], sea slug [84], sea hare [85], squid [86], cod, plaice, salmon [87], tuna dark muscle [88], Nemipterus japonicas backbone [89], and shrimp shell [90]. Moreover, Wergedahl et al. have revealed that protein glycoalysate of salmon was able to reduce the risk of cardiovascular diseases via lowering plasma cholesterol level and inhibiting the activity of Acyl-CoA:cholesterol acyltransferase in Zucker rats [91].

Obesity, an excessive body weight in the form of fat, has become one of the serious public health problems. This epidemic poses a risk for several diet-related chronic diseases including type 2 diabetes, cardiovascular disease, hypertension and stroke, certain forms of cancer and sleep-breathing disorder [92]. Therefore, several lines of studies have provided evidence to finding the efficient agents and potential targets for anti-obesity therapeutics. Herein, cholceystokinin, a biomarker associated with satiety, is identified as a promising target to reduce obesity [93]. Meanwhile, low molecular weight peptides (1-1.5 kDa) from shrimp head protein hydrolysates have been found to be an effective agent for stimulation of cholecystokinin release in STC-1 cells [94]. Thus, these

### Table 3

<table>
<thead>
<tr>
<th>Source</th>
<th>Peptide name</th>
<th>Potency</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyster</td>
<td>LLEYSI</td>
<td>IC50: 15 nM</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>LLEYSI</td>
<td>20 nM</td>
<td>[72]</td>
</tr>
<tr>
<td>Marine sponge</td>
<td>Mirabamide A</td>
<td>IC50: 0.04 and 0.14 μM</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Mirabamide C</td>
<td>IC50: 0.14 and 1.3 μM</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Mirabamide D</td>
<td>IC50: 0.19 and 3.9 μM</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Theopapuamide B</td>
<td>IC50: 0.8 μg/ml</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>Celebeside A</td>
<td>IC50: 1.9 μg/ml</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>Homophymin A</td>
<td>IC50: 75 nM</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>Neamphamide A</td>
<td>EC50: 28 nM</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>Callipeltin A</td>
<td>EC50: 0.01 μg/ml</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td>Papuamide A and B</td>
<td>EC50: 4 μg/ml</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>Microinosamidase</td>
<td>EC50: 0.2 μg/ml</td>
<td>[79]</td>
</tr>
</tbody>
</table>

IC50: 50% inhibitory concentration; EC50: 50% effective concentration.
peptides are suggested as an promising functional food against obesity via regulation of cholecystokinin release.

Blood flow properties play an unambiguous role in thrombogenesis [95]. Blood coagulation is processed by coagulation factors in order to stop the flow of blood though the injured vessel wall whenever an abnormal vascular condition and exposure to non-endothelial surfaces at sites of vascular injury occur. As endogenous or exogenous anti-coagulants interfered with the coagulation factors, the blood coagulation can be stopped. These anti-coagulants have been used for therapeutic purposes, for example, a cure for hemophilia [96]. Although the anti-coagulant marine peptides have rarely been reported, they have been found from marine organisms such as marine echiurid worm [97], starfish [98], and blue mussel [99]. Moreover, marine anti-coagulant proteins have also been purified from yellowfin sole [100] and ark shell [101]. These marine derived anticoagulant peptides are non-cytotoxic and have potential to use as functional ingredients in nutraceuticals or pharmaceuticals.

Components which bind and solubilize minerals such as calcium can be considered to be beneficial in the prevention of dental caries, osteoporosis, hypertension and anemia [102]. Notably, some peptides derived from hoki and Alaska pollack frame proteins have been known due to their calcium-binding capability [103–105]. Moreover, the improved calcium retention with hoki phosphopeptide intake was observed in osteoporosis-model rats to the same level as a commercially prepared casein oligosaccharide-peptide preparation [106]. Calcium-binding peptides derived from marine may have applications as dairy free functional food or beverage ingredients for people with lactose intolerance, anti-carcinogenic ingredients as agents for reducing the risk of osteoporosis.

4. Conclusion

It is assumed that much attention has been paid recently by researchers toward marine compounds as the safe and efficient agents in prevention or treatment of chronic diseases. Consequently, a large number of bioactive agents from marine organisms have been identified based on the specific assay system or screening approach. Interestingly, marine peptides have been found due to their various biological activities and health beneficial effects. Moreover, the extensive studies marine organisms-derived peptides will contribute to the generation of novel functional food as well as pharmaceutical products. Thus, marine peptides are believed as a valuable source of bioactive compounds which could be introduced for the development of food and pharmaceutical industries.

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References
