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Review Article

# Anti-oxidative, Anti-inflammatory, Anti-diabetic and Anti-ACE Hydrolysates Derived from Fish Protein: A Review of Multifunctional Peptides

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## Abstract

Bioactive compounds have widely studied to reduce risk of cardiovascular disease on human's health. In recent years, much attention has been paid to the existence of peptides with biological activities and hydrolysates derived from foods. This paper presents a review of the oxidative stress and hypertension that occurred in the human and food system. Antioxidant and antihypertension peptides isolated from fish sources may be used as functional ingredients in food formulations to promote consumer's health and improve the shelf life of food products. In addition, the antioxidant and antihypertension peptides derived from various food proteins, particularly from fish, have been discussed. Furthermore, the bioactive peptides may exist as multifunctional peptides which can exert more than one biological activity.

***Keywords:*** *Bioactive Peptide; Fish Protein; Antioxidant; Anti-ACE; Multifunctional Peptide*

## Abbreviations

ROS: Reactive Oxygen Species; ACE: Angiotensin Converting Enzyme; RAS: Renin-Angiotensin System; Ang: Angiotensin; PDE: Cyclic Nucleotide Phosphodiesterase; cAMP: Cyclic Adenosine Monophosphate

## Introduction

Definition of health has no longer been restricted to the absence of disease but may include physical fitness as well as mental and physiological well-being. Food is required for development, growth and maintenance of the body, but food is also recognized to play a key role in the quality of life. In food pyramid, meat as a source of protein, has been categorized as food protein with chicken, fish and egg. Among all of meat protein, fish has the highest biological value than others. Besides supplying amino acids and energy that is essential for growth and maintenance, food proteins may act as an important source of bioactive peptides. Bioactive peptides are referred to specific protein fragments that have specific bioactive activities and involved in the improvement of health qualities [1,2]. Upon oral administration, bioactive peptides may affect the major body systems which involved cardiovascular, digestive, immunes and nervous system, depending on their amino acid sequence and their own specific target. In addition, the peptides must reach the cardiovascular system in an intact form (e.g. not being affected by digestive human proteases).

The bioactive peptides are inactive within the sequence of native proteins. The peptides of interest can be released by proteolytic hydrolysis: either with the used of enzyme(s), proteolytic microorganism or fermentation [3]. Findings of natural peptides with anti-oxidants and anti-hypertensive activities have been widely studied to cope with cardiovascular disease which affect people almost around the world, mostly in the advanced technology countries. In this paper, the oxidation process and renin-angiotensin system in relation to hypertension were discussed in effort to improve the findings of natural source of bioactive components towards health improvement. This review centers on multi-functional peptides from source of fish with properties relevant to oxidative stress, inflammation, diabetic and hypertension illnesses.

### Oxidation process, free radicals and antioxidative peptides

Lipid oxidation which strongly related to oxidative stress in human cells had been associated with many serious diseases such as cancer, hypertension, diabetes and cardiovascular disease [4]. In food product, the oxidation of protein is affected by lipid oxidation as well, when the products of lipid oxidation react with proteins, which causes their subsequent oxidation [5]. On the contrary, carbohydrate is less sensitive to oxidation than lipid and protein [6]. In foods, highly reactive molecules generated through these chemical processes are responsible for producing unpleasant and obnoxious odors and flavors in rancid foods and oils. These chemical processes may also destroy nutrients in food [7]. The oxidation processes are primarily occurring on unsaturated fats by a free radical-mediated process. The radicals can interact with molecular oxygen and hydrogen atom to form lipid peroxy radicals and hydroperoxide and further new lipid radicals. These radicals will cause the acceleration and continuation of the chain reaction, especially at a higher temperature [8]. Eventhough, the oxidation process is vital in various life processes, mainly in aerobic vertebrates and human [9,10], which lead to the formation of reactive oxygen species (ROS) as the side-products. The ROS are including free radicals (such as superoxide anion, hydroxyl) and non-free radical species (such as hydrogen peroxide and singlet oxygen).

Antioxidants can reduce the ROS species by donating a hydrogen atom or an electron to radicals formed from unsaturated lipids. The antioxidant component can terminate the oxidation-chain reaction by removing initiators or radical intermediates from the medium. Antioxidants play a vital role in both human as well as food system to reduce the oxidative radical species. In human body, endogenous antioxidants can help minimize the radicals to protect tissues and organs from the oxidative damages. These endogenous antioxidative components are include enzymes (such as superoxide dismutase, catalase, and glutathione peroxidase) and various non-enzymatic compounds (such as selenium, α-tocopherol, and vitamin C) [11]. In addition, charged proteins, peptides and amino acids can also contribute to the antioxidative capacity towards maintaining the health of biological tissues [12]. However, the antioxidant-prooxidant balance in human body can change due to factors, such as fatigue, environmental pollutants, excessive caloric intake, high fat diets and with the progression of age [13,14]. In food systems, antioxidants are useful in neutralizing the lipid peroxidation product, and thus help to maintain texture, flavor and color of the food product during storage [15].

Dietary antioxidants has been recognized as potentially effective to increase the body's antioxidant load. Synthetic antioxidants have been suspected of being responsible for toxicity in human body in the long term. Hence, interest on the findings of natural antioxidants has increase, especially peptides derived from food proteins. Natural antioxidants from plant-based such as tocopherols, vitamin C, herbal extracts like rosemary and sage, as well as tea extracts have already been commercialized as alternatives to synthetic antioxidants in food systems [16]. Recent literature has given much attention to determine and identify the antioxidative potential of peptides derived from various food sources and potential applications as functional foods and nutraceuticals. Bioactive peptides derived from sources like soy, milk, egg, and fish have also been shown to exhibit antioxidant activity in various muscle foods [17]. Protein hydrolysates with antioxidant properties can be a replacement to the synthetic antioxidant for the pharmaceutical, health food, as well as the food processing and preservation industries. *In vitro* studies such as in scavenging the radical species indicated the potential of these food-derived peptides to act as antioxidative agents to control various oxidative processes in the human as well as in food system [18].

### Renin-angiotensin system, hypertension and Anti-ACE peptides

Angiotensin-converting enzyme (ACE) is important in regulation of normal blood pressure, cardiovascular function and electrolyte balance [19]. High blood pressure, or hypertension, is a condition of sustained increase in blood pressure levels and is the primary risk factor for cardiovascular disease (CVD). CVD, a class of diseases that affect the blood vessels and the heart, has been recognized as one of the causes of death worldwide including Malaysia [20]. Hence, the inhibition of ACE is a useful therapeutic approach in the treatment of hypertension [21].

Intravascular renin-angiotensin system (RAS) is involved in maintaining blood pressure homeostasis and fluid and salt balance, whereas the tissue RAS is involved in pathological and physiological processes, such as tissue growth, development and inflammation. In RAS, substrate angiotensinogen from the liver which released into the circulation, is degraded by the enzyme renin, generating inactive angiotensin I (Ang I). When this peptide interacts with the ACE, the reaction giving rise to angiotensin II (Ang II): a vasoconstrictor. Through interactions with specific receptors, Ang II stimulates a wide variety of signaling pathways in the blood vessels, heart, adipose tissue, pancreas, kidney, and brain. Due to the function of directly generating Ang II, ACE has been focused for RAS studies since its discovery [22].

Specific ACE inhibitors have been developed which are used in the treatment of hypertension and congestive heart failure [23]. Three types of synthetic ACE inhibitors were designed which are captopril, enalapril and lisinopril as one type, and fosinopril; they are grouped by their ligand for the active site on ACE. Captopril has a sulfhydryl moiety, enalapril and lisinopril have a carboxyl moiety, and fosinopril has a phosphorus group [24]. These synthetic ACE inhibitors are in the current used in the treatment of hypertension in humans [25]. Although these synthetic inhibitors show a remarkable effect in treating hypertension, these synthetic ACE inhibitors are known to have strong side effects, such as cough (the most common problem), skin rashes and angioedema [26]. Thus, the development of safe and natural ACE inhibitors is necessary for future treatment and prevention of hypertension.

Many studies have successfully produced and isolated ACE inhibitory peptides from various food proteins: include animal and plant based [27,28]. Among the bioactive peptides generated from meat protein, peptides with ACE inhibitory activity have been widely studied [29,30]. Ghassem., *et al.* [31] found two ACE inhibitory peptides from myofibrillar protein hydrolysate of Haruan fish (*Channa striatus*) and have been identified as VPAAPPK and NGTWFEPP. The two proline residues at the C-terminal sequence was determined to be responsible for the high ACE inhibitory activity of these peptides. Food-derived Val-Ala-Pro (VAP) tripeptide from grass carp protein hydrolysates having the properties of ACE inhibitor has been first reported by Chen., *et al* [32]. These peptides also stable against both ACE and gastrointestinal enzymes (pepsin and chymotrypsin).

### Multifunctional peptides

Some bioactive peptides have an extra benefit of being multifunctional, with the ability to have two or more different bio-activities. For example, captopril, the synthetic ACE inhibitor, can act as an antioxidant agent as well [33]. Multifunctional hydrolysates having both antioxidant and ACE inhibitory activities were reported in egg white protein hydrolysates [34], commercial fermented milk in Europe [35] and extracts of chum salmon cartilage and skin [36]. Bioactive peptides with both antioxidant and anti-ACE properties were also found from red tilapia protein hydrolysate [37]. In addition, Davalos., *et al*. [34] identified a multifunctional peptide with sequence Tyr-Ala-Glu-Glu-Arg-Tyr-Pro-Ile-Leu, which shows high radical scavenging and strong ACE inhibitory activities. Furthermore, the peptide with ability to exert the combination of antioxidant and ACE inhibition activities could be very useful for the control of cardiovascular diseases.

Contraction and relaxation of cardiac myocytes and vascular smooth muscle are controlled by cyclic nucleotide phosphodiesterase (PDE) enzyme for signal transduction via second messengers ($Ca^{2+}$ and cAMP). Disturbance in the component of the signaling pathway could lead to disease progression such as development of cancer or hypertension related to $Ca^{2+}$-induced changes in membrane functions [38]. The studies on structure and activity of bioactive peptides demonstrated the importance of charged amino acids in the potency of peptides as CaMPDE inhibitors and antioxidants [39,40]. Findings by You., *et al.* [41] on the peptides from hen's egg white lysozyme showed moderate CaMPDE inhibitory activities and free-radical scavenging properties. On the other hand, Rao., *et al.* [42] have found bioactive peptides with ACE inhibitory and antioxidant activities from the hen's egg white lysozyme-derived peptides. Multifunctional nature of antioxidants peptides, for example having the ability to impart other bioactivities such as anti-CaMPDE, anti-ACE, opioid and cholesterol lowering capacity [34-36,41,43], may become much attractive candidates than non-peptidic antioxidants as functional food ingredients in promoting human's health.

### Traditional and fermented functional fish-based products of Asia

Fermented foods have been generally used among the Asian people, especially Southeast Asian people. They are known for several health benefits. During food fermentation by proteolytic microorganisms, bioactive peptides can increase [44,45]. Therefore, the fermentation of food materials enhances the biological properties of food products. Fish products (such as Budu, Pekasam, Chenchalok, Funazushi, Hongeohoe, Bagoong, Sikhae and Pla ra) are habitually consumed by Malaysian, Thai, Indian, Chinese, Vietnamese, Korean, Japanese and Taiwanese people. The fermented foods are prepared by natural fermentation, traditionally. In Asian countries, the fermented food is made using lactic-acid bacteria (LAB) [46,47]. Several industrial dairy starter cultures are used for microbial fermentation of food proteins. Generally employed probiotic LAB strains are *Lactobacillus casei, L. plantarum, L. brevis, L. pentosus, L. fermentum, L. paracasei, Weissella koreenis, W. cibaria, W. confusa, L. fallax, L. mesenteroides, Leuconostoc kimchi, Enterococcus* and *Pediococcus spp.*

ACE-inhibitory activities of fermented food products such as salmon fish sauce [48] and fermented blue mussel sauce [49] have been reported. Okamoto., *et al.* [48] have investigated angiotensin I-converting enzyme inhibitory activity of fish sauce obtained from salmon in Japan. Two fractions were identified with the strongest ACE inhibitory activity. Oral administration of these peptides to spontaneously hypertensive rat displayed a hypertensive effect. Studies by Je., *et al.* [49] have showed that fermented blue mussel sauce contained ACE inhibitory bioactive peptides. The blue mussels were fermented with 25% NaCl (w/w) at 20°C for 6 months. The resultant mixture was passed through a 40-mesh sieve, desalted using an electro-dialyzer and then lyophilized. An ACE inhibitory peptide (EVMAGNLYPG) was purified and evaluated for antihypertensive effect in spontaneously hypertensive rats following oral administration. After peptide ingestion, the blood pressure was significantly decreased.

In another study, antioxidant activity of fermented fish products has been investigated for various products such as blue mussel sauce [50], fermented fish mussel sauce [51], hydrolysed and fermented minced mackerel [52]. Traditional Japanese fermented sardine with rice bran was assessed for antioxidant constituents using linoleic acid model system. Strongest antioxidant fraction was estimated to be about 3.9 kDa [53]. Based on the studies by Najafian and Babji [54,55], antioxidant peptides of two fermented products from freshwater fish, namely Budu and Pekasam, were identified. Budu (fish sauce) is obtained through spontaneous hydrolysis by endogenous enzymes and microorganisms [56]. Fish sauce is an important part of the diet of people in Southeast Asian countries, but it is more important as supplements the diets of the poor communities with high-quality proteins and vitamins [57]. Budu is made by mixing anchovy fish with salt and fermented for 3 - 12 months and is served as a condiment [58]. Some factories add other ingredients, including coconut sugar and tamarind. With endogenous enzymes and fermentation of fish, peptides derived from protein hydrolysate may possess different amino acid sequences [59]. Fermentation also leads to an improvement in increases protein content and amino acid balance [60].

Najafian and Babji [54,55] have prepared Budu from fresh anchovy fish and measured the antioxidant activity. Budu extract exhibited scavenging activities for DPPH and ABTS radicals as well as reducing power. After purification, two peptide sequences which have the antioxidant activities, LDDPVFIH and VAAGRTDAGVH, were found. The presence of the hydrophobic amino acids' isoleucine, valine, leucine, proline, phenylalanine, acidic amino acids (aspartic acid) and glycine in the peptide sequences can contribute to the high antioxidant activity in the Budu extract. Thus, Budu may serve as source of novel peptides for natural antioxidants in a food product. Pekasam is a fermented fish product from Malaysia produced with fermentation of lactic acid bacteria. It is prepared from freshwater fish such as loma, lampam, tengalan and tilapia. Najafian and Babji [54,55] have purified bioactive peptides from pekasam which showed the antioxidant effects and two novel peptides, IAEVFLITDPK and AIPPHPYP, were identified. The identified peptides were rich in hydrophobic (isoleucine, alanine, valine and proline), acidic (aspartic acid and glutamic acid) and basic (lysine) amino acids that can contribute to the antioxidant properties. From the conducted studies, bioactive peptides derived from fermented fish can be used in the pharmaceutical and nutraceutical industry to extend new medicinal and functional food (in improving public health and preventing ROS-related chronic diseases) with antioxidant effects.

## Conclusion

Recent studies have shown that food-derived bioactive peptides play a vital role in human health and nutrition. Fish-derived bioactive peptides with multifunctional properties may have potential for use as food ingredients, nutraceuticals and pharmaceuticals ingredients. They may be a better substitute for synthetic chemicals. Anti-ACE peptide can be used as a substitute for synthetic drugs commonly used to treat hypertension and may have a potential to be natural and healthy ingredients as source of ACE inhibitors. Based on the evidence demonstrating their beneficial health effects, multifunctional fish-derived bioactive peptides have much higher benefits to be used as bioactive ingredients in functional foods, food supplements and in the pharmaceutical industries.

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## Conflict of Interest

The authors declare that there are no conflicts of interest.

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