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Bioactive peptides from meat and their influence on human health

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A b s t r a c t: Bioactive peptides are functional components, encrypted in the proteins and can be derived from food of plant and animal origin, including meat. After releasing during gastrointestinal digestion or food processing, these peptides exhibit many different effects on human body such as antioxidative, antimicrobial, antihypertensive, antithrombotic, cytomodulatory, immunomodulatory, anticancer, hypocholesterolemic and anti-obesity effects, which mainly depends on their structure and other properties. Considering bioactive activities of these peptides and their beneficial influence on health on one side, and millions of deaths caused by cancer, cardiovascular and other diseases associated with lifestyle on the other side, it is obvious that these peptides can be used for health promotion and disease risk reduction, especially because they have some advantages compared to synthetic drugs.

***Key words**: functional food, ACE inhibitory peptides, muscle proteins, antioxidant and antibacterial activity.*

Introduction

Cardiovascular diseases, cancer, diabetes and obesity are responsible for millions of deaths worldwide annually, and present increasing health and economic problem as well (*Murray and Lopez,* 1997; *CDC*, 2005; *Ahhmed and Muguruma*, 2010; *DHHS*, 2010; *Weiss et al.*, 2010). These diseases and related conditions are also called chronic lifestyle-related diseases, because they are associated not only with heredity, but also with changes in lifestyle where diet plays important and in some causes crucial role (*Murray and Lopez*, 1997; *Anand et al.*, 2008; *Ahhmed and Muguruma*, 2010; *Decker and Park*; 2010; *Cam and de Mejia*, 2012). This fact implies that food also may be used in the prevention, control or in some cases treatment of these diseases and this approach may present preventive health care strategy (*Decker and Park,* 2010). Consequently, as a response to this challenge food industry presented a new class of foods, so-called "functional foods", and in Europe, these new food products have been labeled as "novel" foods and food ingredients (*Diplock et al*., 1999; *Weiss et al.*, 2010; *Olmedilla-Alonso et al.*, 2013). This food contains components which exhibit a beneficial physiological effects on human health (*Diplock et al.*, 1999; *Weiss et al.*, 2010; *Olmedilla-Alonso et al.*, 2013). New trend of promoting human health by using bioactive compounds is particularly interesting and presents a great challenge but at the same time opportunity for the meat industry, to improve the quality and image of meat (*Jiménez Colmenero et al.*, 2010; *Jiménez-Colmenero et al.*, 2012; *Olmedilla-Alonso et al.*, 2013). Meat is important in human diet and had a great role in human evolution, especially in brain and intellectual development (*Higgs*, 2000; *Baltić et al.*, 2002; *Pereira and Vicente*, 2013). Also, meat presents a valuable source of proteins, conjugated linoleic acid, antioxidants, vitamins such as riboflavin, niacin, vitamin B_6, pantothenic and folic acid and numbers of minerals including iron, zinc, selenium and phosphorus (*Jimenez-Colmenero et al.*, 2001; *Baltić et al.*, 2002; *Chan*, 2004; *Mulvihill*, 2004; *Biesalski*, 2005; *Arihara and Ohata*, 2006; *Descalzo and Sancho*, 2008; *Ahhmed and Muguruma*, 2010; *Decker and Park*, 2010; *Marković et al.*, 2010; *Weiss et al.*, 2010; *Toldra and Reig*, 2011; *Baltić et al.*, 2013; *Pereira and Vicente*, 2013). Meat proteins are not only important source of essential amino

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acids, but of biactive peptides as well, and number of studies are focusing on the development of functional biopeptides from this source (*Udenigwe and Ashton*, 2013; *Weiss et al.*, 2010; *Young et al.*, 2013).

Peptides - sources and production

Bioactive peptides are short, approximately 2–20 (in some cases this range can be extended) amino acids sequences with molecular masses of less than 6 kDa (*Möller et al.*, 2008; *Shahidi and Zhong*, 2008; *Di Bernardini et al.*, 2011**).** They are food derived components, and can be obtained from different plant and animal sources (*Ryan et al.*, 2011). A great number of bioactive peptides are derived from plants such as soy, pulses (lentil, chickpea, pea and beans), oat, wheat, rice, maize, sunflower, hemp seed, pumpkin, canola, flaxseed and many others including mushrooms (*Hartmann and Meisel*, 2007; *Möller et al.*, 2008; *Rutherfurd-Markwick*, 2012; *Udenigwe and Aluko*, 2012; *Saavedra et al.*, 2013). Although most peptides derived from animal sources are generated from milk and milk-based products proteins, peptides also were isolated from eggs, bovine blood, collagen, gelatin, various fish species including tuna, sardine, herring, salmon, bonito and from marine organisms (*Möller et al.*, 2008; *Shahidi and Zhong*, 2008; *Ryan et al.*, 2011; *Di Bernardini et al.*, 2011; *Najafian and Babji*, 2012; *Ngo et al.*, 2012; *Rutherfurd-Markwick*, 2012; *Udenigwe and Aluko*, 2012; *Saavedra et al.*, 2013). Being a major source of high quality proteins, meat presents one of the most investigated sources for isolation of bioactive peptides in recent number of years (*Ryan et al.*, 2011). In addition, it's not only myosin and actin which are used for peptides generation, but other proteins from thick and thin filaments, and connective tissue proteins like fibrillar collagen, as well (*Udenigwe and Ashton*, 2013).

Bioactive peptides can be generated from protein precursors by different methods including digestive proteolysis in the gastrointestinal tract, chemical or enzymatic hydrolysis *in vitro* during food processing, and microbial fermentation (*Korhonen and Pihlanto*, 2006; *Möller et al.*, 2008; *Shahidi and Zhong*, 2008; *Ryan et al*., 2011; *Agyei and Danquah*, 2012; *Rutherfurd-Markwick*, 2012). In recent years a new method based on molecular genetic engineering, has been reported and it is also possible to synthesize the peptide by chemical or enzymatic synthesis if amino acid sequence is known (*Korhonen and Pihlanto*, 2006; *Shahidi and Zhong*, 2008; *Hernández-Ledesma et al.*, 2011; *Agyei and Danquah*, 2012). Each of these methods has some advantages or disadvantages, which should be considered when selecting one or several combined methods for a certain purpose (*Shahidi and Zhong*, 2008). Use of acid hydrolysis in order to release some peptides is economic, relatively simple to perform, but at the same time difficult to control and can damage certain amino acids. Moreover, selectivity and specificity of this chemical hydrolysis is low, which is why this method is rarely used (*Shahidi and Zhong*, 2008; *Rutherfurd-Markwick*, 2012). Methods based on enzymatic hydrolysis have an advantage because they are more predictable with respect to the end products, and the process conditions can be controlled. Because of that, these are commonly used methods for peptide production in laboratories and industry. Enzymes which are used in this technique can be obtained from plants, microorganisms or animals, and can be used alone or in combination with other enzymes, in order to simulate the fate of a protein in *in vitro* condition (*Shahidi and Zhong*, 2008; *Agyei and Danquah*, 2012). There are a number of proteinases including trypsin, subtilisin, chymotrypsin, thermolysin, pepsin, proteinase K, papain alcalase, pronase, papain, carboxypeptidase A, pancreatin and commercial products such as Alcalase Flavourzyme and Neutrase which are used for peptide preparation (*Korhonen and Pihlanto*, 2006; *Shahidi and Zhong*, 2008; *Agyei and Danquah*, 2012; *Udenigwe and Ashton*, 2013). It is important that isolation of peptides by enzymatic hydrolysis is performed under respective optimal conditions of enzyme (temperature, pH, time course, etc.) for better results (*Shahidi and Zhong*, 2008; *Agyei and Danquah*, 2012).

Enzymatic hydrolysis of protein is the technique mostly used for isolation of peptides from meat sources, and the digestive enzymes which are most commonly used are pepsin, trypsin and chymotrypsin (*Ryan et al.*, 2011). Although bacterial fermentation presents valuable method for isolation of bioactive peptides from milk proteins, it wasn't successful in obtaining peptides from meat source, probably because of poor proteolytic activity of the *Lactobacillus spp.* used in meat fermentations (*Ryan et al.*, 2011).

Hydrolysate obtained after the application of one of the previously mentioned methods, presents a mixture mainly composed of peptides and amino acids. Several methods can be used for separation of bioactive peptides from hydrolysate (*Ryan et al.*, 2011; *Agyei and Danquah*, 2012; *Najafian and Babji*, 2012). Ultrafiltration membrane system is a method which can be used in order to fractionate hydrolysates based on peptide size and obtained peptides with desired molecular weights (*Ryan et al.*, 2011; *Najafian and Babji*, 2012). More precise method is nanofiltration (*Najafian and Babji*, 2012). For the same purpose, ion exchange, gel filtration technologies, liquid chromatography (HPLC), reversed-phase liquid chromatography (RP-HPLC), and gel permeation chromatography could be used (*Pedroche et al.*, 2007; *Chabeaud et al.*, 2009; *Agyei and Danquah*, 2012). For strongly charged biomolecules electro-membrane filtration (EMF) can be beneficial technique (*Agyei and Danquah*, 2012). Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometric analysis is also utile method (*Najafian and Babji*, 2012). These methods can be used separately, but combination of two or more methods for production and isolation of peptides may be required (*Agyei and Danquah*, 2012). It has been reported that HPLC is commonly used with a UV detector or mass spectrometer (*Najafian and Babji*, 2012). Individual peptide fractions can be identified by using the combined techniques of mass spectrometry and protein sequencing, while liquid chromatography followed by tandem mass spectrometry detection (LC–MS/MS) or conventional membrane filtration with electrophoresis also can be applied (*Ryan et al.*, 2011; *Agyei and Danquah*, 2012; *Najafian and Babji*, 2012).

Although, inactive within the sequence of the protein, after the releasing described above, , bioactive peptides may induce many beneficial effects on human body (*Möller et al.*, 2008; *Korhonen and Pihlanto*, 2006; *Di Bernardini et al.*, 2011; *Agyei and Danquah*, 2012). Their properties were investigated under *in vitro* and *in vivo* conditions, and it has been reported that food derived bioactive peptides have antioxidative, antimicrobial, antihypertensive, antithrombotic, cytomodulatory, anticancer, immunomodulatory, opioid agonistic, mineral binding, hypocholesterolemic and anti-obesity effects. In addition, many of bioactive peptides possess multifunctional properties (*Korhonen and Pihlanto*, 2006; *Möller et al.*, 2008; *Shahidi and Zhong*, 2008; *Di Bernardini et al.*, 2011; *Ryan et al.*, 2011; *Agyei and Danquah*, 2012; *Udenigwe and Ashton*, 2013). The activity of bioactive peptides depends on amino acid composition and sequence (*Shahidi and Zhong*, 2008). Moreover, compared to conventional small molecules, these peptides have high bioactivity, act on specific targets inside the body, have low levels of toxicity and they don't accumulate in small amounts in the tissues, which is why many researchers investigate their functional properties and potential applications (*Marx*, 2005; *Agyei and Danquah*, 2012).

Antihypertensive properties

Hypertension is an increasing health problem which affects one third of the worldwide adult population, both men and women, especially in developed countries, and presents the most common type of cardiovascular disease (*Ahhmed and Muguruma*; 2010; *Hong et al.*, 2008; *Shahidi and Zhong*, 2008; *Hernández-Ledesma et al.*, 2011; *He et al.*, 2013). High blood pressure is predominant factor which contibutes to cardiovascular diseases including myocardial infarction, heart failure, coronary heart disease, peripheral artery disease, stroke kidney failure, blindness, end-stage diabetes and even dementia (*Hong et al.*, 2008; *Ahhmed and Muguruma*, 2010; *Hernández-Ledesma et al.*, 2011; *Ryan et al.*, 2011; *Sharp et al.*, 2011; *Rutherfurd-Markwick*, 2012; *He et al.*, 2013). It is one of the main causes of the premature death, and WHO estimates that by 2020, heart disease and stroke will become the leading causes of death and disability worldwide (*Erdmann et al.*, 2008; *Onuh et al.*, 2013). There are a number of antihypertensive medications like captopril and analapril on the market, but apart from their adventages, their use may cause some side effects including coughing, taste disturbances, skin rashes, angio-oedema and many other disfunctions of human organs (*Wu et al.*, 2008; *Ahhmed and Muguruma*, 2010; *Ryan et al.*, 2011). Also, these drugs are expensive, and only in the USA, cost of antihypertensive drug annualy is approximately $15 billion (*Hong et al.*, 2008). As a results, over the last two decades, numerous researchers have investigated some effective natural alternitives which would be less expensive for production and cause no side-effects. One of such possibility is the use of food derived bioactive peptides which exhibit antihypertensive effect (*Shahidi and Zhong*, 2008; *Wu et al.*, 2008 ; *Ahhmed and Muguruma*, 2010; *Hernández-Ledesma et al.*, 2011; *Ryan et al.*, 2011).

Bioactive peptides act differently then hipotensive drugs. Synthetic substances directly block action of ACE (angiotensin-converting enzyme) responsible for converting angiotensin-I into angiotensin-II, major product of the renin–angiotensin system which presents a powerful vasoconstrictor. ACE hydrolyze bradykinin, a potent vasodilator, also induces the release of aldosterone in the adrenal cortex, which results in increasing of sodium concentration and blood pressure (*Wu et al.*, 2008; *Ahhmed and Muguruma*, 2010; *Hernández-Ledesma et al.*, 2011; *Cam and de Mejia*, 2012; *Escudero et al.*, 2012; *He et al.*, 2013; *Udenigwe and Ashton*, 2013). Mechanism of action of ACE inhibitory peptides is based on competing with ACE and preventing the production of angiotensin-II, causing relaxation of the arterial walls and reduction of fluid volume, in which way these biactive peptides improve heart function and increase blood and oxygen flow to the heart, liver, and kidneys (*Ahhmed and Muguruma*, 2010; *Ryan et al.*, 2011; *He et al.*, 2013). ACE inhibitory peptides may bind to the active site of the ACE enzyme, or to an inhibitor site located on the ACE enzyme, and in this way change the protein confirmation and prevent the angiotensin-I from binding to the enzyme active site (*Wijesekara and Kim*, 2010; *Ryan et al.*, 2011). Futhermore, some studies show that food-derived bioactive peptides can also inhibit the activity of renin, and in that way induce a reduction of blood pressure (*Udenigwe and Aluko*, 2012). There are three groups of ACE inhibitory peptides: true inhibitor type, substrate type and pro-drug type, and their classification is based on their inhibitory activity following preincubation with ACE (*Iroyukifujita et al*., 2000; *Arihara and Ohata*, 2006; *Ryan et al*., 2011).

Structure characteristics of peptides are associated with their antihypertensive properties. ACE-inhibitory peptides are mostly peptides with short amino acid sequences containing from 2 to 12 amino acids. *Saiga et al.*, (2003) found that presence of hydroxyproline is crucial for binding of peptides and ACE in cases when peptides contain more than three amino acids in length. Many studies showed that C-terminal of ACE-inhibitory peptides usually contains hydrophobic amino acids residues and that these residues have a crucial role in competitive binding to the active site of ACE (*Hernández-Ledesma et al.*, 2011; *Ryan et al.*, 2011). It has been reported that ACE-inhibitory peptides with the highest antihypertensive activity contain aliphatic, basic and aromatic residues, at the penultimate positions, and aromatic, proline and aliphatic residues at the end of *C*-terminal. This is explained by interaction of these residues with the three hydrophobic sub-sites located on the active site of ACE (*Matsufuji et al.*, 1994; *Iroyukifujita et al.*, 2000; *Ono et al.,* 2003; *Hayes et al.*, 2007; *Qian et al.*, 2007; *Hernández-Ledesma et al.*, 2011; *Ryan et al.*, 2011). For the same reason, hydrophilic peptides are incompatible with the active sites of ACE, and exhibit none or a weak ACE inhibitory activity (*Li et al.*, 2004; *Matsui and Matsumoto*, 2006; *Ryan et al.*, 2011). Studies found that *N*-terminal end of the peptides with ACE-inhibitory activity is hydrophobic (*Hayes et al.*, 2007; *Rho et al.*, 2009; *Ryan et al.*, 2011). Moreover, it has been found that amino acid at the position three from the C-terminal requires the L-configuration (*Hernández-Ledesma et al.*, 2011).

Numbers of peptides with ACE-inhibitory activity were isolated from porcine, beef and chicken muscles. Commonly used methods for the evaluation of ACE-inhibitory effects of bioactive peptides in *in vitro* conditions are those based on spectrophotometric and high-performance liquid chromatography (HPLC) assays (*Vermeirssen et al.*, 2002; *Li et al.*, 2005; *Shalaby et al.*, 2006; *Siemerink et al.*, 2010; *Hernández-Ledesma et al.*, 2011). Studies conducted in *in vivo* systems, are generally based on oral or intravenous application of purified peptides to spontaneously hypertensive rats and measuring of blood pressure immediately after application or after a certain time (*Ahhmed and Muguruma*, 2010; *Hernández-Ledesma et al.*, 2011). Also, in some experiments for investigation of antihypertensive peptides properties normotensive Wistar-Kyoto rats were used (*Hernández-Ledesma et al.*, 2011). *Arihara et al*. (2001) generated two ACE-inhibitory peptides with amino acid sequence MNPPK, and ITTNP known as from porcine myosin. These peptides were orally applied to spontaneously hypertensive rats (SHR) in order to investigate their effect on systolic blood pressure (SBP). 24 h after oral administration, the SBP of both test groups was still significantly lower than that of the control group, which proved that peptides exhibit antihypertensive effect *in vivo* (*Nakashima et al*, 2002; *Ryan et al.*, 2011). MNPPK known as myopentapeptide A, is a precursor to tripeptide MNP which exhibited greater antihypertensive activity (*Udenigwe and Ashton*, 2013). Moreover, M6 peptide with amino acid sequence KRVITY, derived from porcine myosin B by pepsin treatment, showed antihypertensive effect after orall administration to SHR. Maximum decrease of 23 mmHg was noted 6 h after application, and this peptide retained his ACE-inhibitory activity even after thermal process (98 °C for 10 min), (*Muguruma et al.*, 2009; *Ryan et al.*, 2011). In other study, octapeptide with amino acid sequence VKKVLGNP also exhibited ACE-inhibitory effect and caused decrease of SBP in *in vivo* conditions after oral application to SHR (*Katayama et al.*, 2007). *Katayama et al.* (2007) derived two bioactive peptides from porcine troponin. From troponin C they isolated nine amino acids peptide with sequence RMLGQTPTK, and from crude porcine troponin, peptide with the amino acid sequence KRQKYDI. These antihypertensive peptides are categorized as a non-competitive inhibitor and substrate type inhibitor, respectively (*Katayama et al.*, 2003; *Katayama et al.*, 2004; *Katayama et al.*, 2008; *Ryan et al.*, 2011).

Apart from peptides isolated from myosin and troponin, other meat proteins also present valuable sources for generating peptides with antihypertensive activity. One anti-hypertensive peptide with amino acid sequence RPR was isolated from pork nebulin, while two antihypertensive peptides with amino acid sequences KAPVA and PTPVP were isolated from pork titin protein by *Escudero et al*. (2010). Although some of these peptides did not seem to have high ACE-inhibitory activity *in vitro*, they exhibited antihypertensive activity *in vivo*, which was explained by the bioconversion of ACE-inhibitory peptides or by antihypertensive mechanism which could be influenced by these peptides (*Lopez-Fandino et al.*, 2006; *Escudero et al.*, 2012).

In addition, *Castellano et al*. (2013) used a method of lactic acid bacterial (*L. sakei* CRL1862 and *L. curvatus* CRL705) fermentation in order to generate ACE-inhibitory peptides from porcine proteins. In a study conducted by *Terashima et al.* (2010), decapeptide with amino acid sequence VTVNPYKWLP was isolated from the myosin heavy chain of chicken leg meat, and his antihypertensive properties were determined (*Udenigwe and Ashton*, 2013). From three peptides isolated from the chicken breast muscle protein hydrolysates by *Saiga et al.* (2003) peptide P4, with amino acid sequence GFXGTXGLXGF exhibited the strongest ACE inhibiting activity with IC value of 42.4 μM, which was higher compared to IC value of 26 μM what was later reported for the peptide by the same authors (*Saiga et al.*, 2006), P4 was categorized as a non-competitive inhibitor of ACE. In the study P4 were administrated intravenous to SHR in doses of 30 mg per kilogram of body weight, and although it caused an immediate decrease in blood pressure it returned to base pressure 60 minutes post administration, which showed that this peptide does not act as a long-term vasodepressor *in vivo* (*Saiga et al.*, 2006; *Ryan et al.*, 2011; *Udenigwe and Ashton,* 2013). *Jang* and *Lee* (2005) generated a peptide with amino acid sequence VLAQYK, from beef sarcoplasmic proteins with ACE-inhibiting IC 23.1 μg/mL. Futhermore, from dry-cured ham it was derived seven dipeptides (RP, KA, AA, GP, AR, GR and RR) which exhibited ACE inhibitory activity with IC_{50} values of 15.2, 31.5, 51.4, 66.0, 95.5, 162.2 and 267 μM, respectively (*Udenigwe and Ashton*, 2013).

Connective tissue also can be a source for obtaining bioactive peptides with hypotensive effects. For example, *Kim et al.* (2001) isolated two ACE-inhibitory peptides, EIIICIII (GPV) and EIIICIV (GPL), from the hydrolysate of bovine skin gelatin which was treated with five proteases (Alcalase, chymotrypsin, Neutrase, Pronase E, and trypsin) in specific order. EIIICIII peptide had an IC_{50} value of 4.7 μM, while the peptide EIIICIV had an IC_{50} value of 2.55 μM (*Kim et al.*, 2001; *Ryan et al.*, 2011). ACE-inhibitory peptides were derived from hydrolysis of chicken collagen as well. At first, collagen was treated by an *Aspergillus oryzae* protease, and then hydrolyzed by treatment with four proteases more (protease FP, protease A, amino G and protease N), after which four oligopeptides were isolated with ACE-inhibitory IC_{50} values of 29,4–60,8 μM. They were administrated to SHR at dose of 3 g/kg body weight and SPB were measured. The greatest reduction occurred 6 h after administration (maximum value of -50 mm Hg), but peptide product showed long-term hypotensive effects *in vivo* (4-week) (*Saiga et al.*, 2006; *Ryan et al.*, 2011; *Udenigwe and Ashton*, 2013). Protein hydrolysates derived by *Onuh et al.* (2013) from chicken skin through alcalase or simulated gastrointestinal digestion showed to possess inhibitory activities against ACE and renin in *in vitro* tests.

Bioactive peptides with ACE-inhibitory activity were isolated and identified from many fish species such as shellfish, tuna, bonito, salmon and sardine (*Yokoyama et al.*, 1992; *Matsufuji et al.*, 1994; *Ono et al.*, 2003; *Qian et al.*, 2007; *Hong et al.*, 2008; *Ahhmed and Muguruma*, 2010; *Ryan*, 2011). Moreover, *Wu et al.* (2008) isolated and identified four peptides (CF, EY, MF and FE) with high ACE-inhibitory activity from shark meat and two of them (EY and FE) have never been reported before.

Antithrombotic properties

Arterial thrombosis often presents a cause or complicate some vascular diseases and conditions like myocardial infarction and stroke. Some peptides obtained from meat sources showed antithrombotic properties and it is considered that their use in the future can be beneficial in the prevention or control of such conditions. (*Udenigwe and Ashton*, 2013). *Shimizu et al*. (2009) isolated a peptide with molecular weight of 2.5 kDa from defatted porcine *musculus longissimus dorsi* and investigated his effect on thrombosis. Pork meat was treated by papain protease and hydrolyzed peptide was implicated orally to mice in doses 210 mg/kg of body weight. After that a carotid artery thrombosis was induced with helium-neon laser and total thrombus size were calculated. Results of this study showed that peptide can significantly inhibit thrombus formation by decreasing platelet activity and have same effect as aspirin administration at 50 mg/kg body weight (*Shimizu et al.* 2009; *Cam and de Mejia*, 2012; *Udenigwe and Ashton*, 2013).

Antioxidant properties

Reactive oxygen species (ROS) and free radicals attack and interact with membrane lipids, protein and DNA in the cell. They can be endogenous or exogenous origin, but in both case have influence on human health and play a great role in ethiology and progression of several diseases including cardiovascular diseases, atherosclerosis, arthritis, diabetes, inflammation, cancer, neuropathies, Alzheimer's and other degenerative diseases as well (*Ames*, 1983; *Esterbauer,* 1993; *Cai et al.*, 2002; *Gimenez et al.*, 2009; *Ryan et al.*, 2011; *Jomova et al.*, 2012; *Udenigwe and Ashton*, 2013). Oxidation by free radicals is also one of the primary mechanisms of quality deterioration in foods and especially in meat products, which also limits shelf-life and makes meat potentially dangerous for consument's health (*Simitzis et al.,* 2009; *Bošković et al.*, 2013; *Udenigwe and Ashton*, 2013). In order to prevent or to retard lipid oxidation, a number of synthetic antioxidants, such as butylated hydroxyanisole (BHA), butylated hydroxutoluene (BHT), tert-butyl hydroquinone (TBHQ) and propyl gallate (PG) are added to food (*Saiga et al.*, 2003a; *Di Bernardini et al.*, 2011; *Ngo et al.*, 2012). Their use may have negative influence on human health which is why food industry tends to find natural alternatives to synthetic antioxidants. (*Saiga et al.*, 2003a; *Sakanaka and Tachibana*, 2006; *Kim et al.*, 2001; *Di Bernardini et al.*, 2011). One of such possibilities is use of peptides from food sources, which have some advantages, compared to synthetic antioxidants. They are considered to be safe for consumers, economic for production, have high activity, they are easy to absorb, also have nutritional value and do not cause immunoreactions like enzymatic antioxidants. The antioxidant effect of peptides was firstly reported by Marcuse in 1960 (*Gómez-Guillén et al.*, 2011). Since then, in order to confirm their antioxidant properties numbers of studies were conducted on peptides from mostly plant and animal sources such as milk, milk-kefir and soymilk-kefir, casein, egg-yolk protein, soybean protein, wheat, potato, rice bran, sunflower protein, leaf protein, peanut kernels, corn gluten meal, frog skin, medicinal mushroom and fungi (*Suetsuna et al.*, 2000; *Peña-Ramos et al.*, 2004; *Sun et al.*, 2004; *Wachtel-Galor et al.*, 2004; *Liu et al.*, 2005; *Zhu et al.*, 2006; *Sakanaka and Tachibana*, 2006; *Li et al.*, 2008; *Megías et al.*, 2008; *Pihlanto et al.,* 2008; *Qian et al.*, 2008; *Xie et al.*, 2008; *Revilla et al.*, 2009; *Hwang et al.*, 2010; *Gómez-Guillén et al.*, 2011; *Ryan et al.*, 2011). In recent years, interest of scientists for peptides from meat, especially fish sources, has increased (*Ryan et al.*, 2011).

In spite of all the research, the exact mechanism of antioxidant activity of peptides still has not been fully understood. Based on current knowledge, it is supposed that peptides are scavengers of free radicals and ROS, they inhibit lipid peroxidation and chelate transition metal ions (*Suetsuna et al.*, 2000; *Wu et al.*, 2003; *Rajapakset al.*, 2005; *Gómez-Guillén et al.*, 2011; *Young et al.*, 2013). In addition, it has been proved that the antioxidant properties of peptides, and especially peptide composition and structure may be affected by a method used to isolate proteins, degree of hydrolysis, type of used protease, peptide concentration and hydrophobicity (*Suetsuna et al.*, 2000; *Saiga et al.*, 2003b; *Peña-Ramos et al.*, 2004; *Erdmann et al.*, 2008; *Liu et al.*, 2010). Type of amino acid, their number in the peptide, as well as the arrangements of amino acid sequence play an important role in antioxidant activity (*Suetsuna et al.*, 2000; *Saito et al.*, 2003a; *Rajapakset et al.*, 2005; *Erdmann et al.*, 2008). Tyr, Trp, Met, Lys, Cys, and His are those amino acids which contribute to antioxidant activity (*Peña-Ramos et al.*, 2004; *Wang et al.*, 2005; *Sarmadi and Ismail*, 2010; *Di Bernardini et al.*, 2011). Histidine-containing peptides possess imidazole group which is considered to be in relation with the hydrogen-donating, lipid peroxyl radical trapping and the metal chelating, while SH group in cysteine has a main role in interaction with free radicals (*Chan et al.*, 1994; *Erdmann et al.*, 2008; *Qian et al.*, 2008; *Sarmadi and Ismail*, 2010). Moreover, it has been found that substitution of L-His by D-His in a peptide leads to reduction of the antioxidative activity, which proves that configuration of amino acids also has influence on antioxidant activity (*Chen et al.*, 1996; *Sarmadi and Ismail*, 2010). Some researchers have found that certain amino acids exhibit higher antioxidative activity when they are incorporated in dipeptides (*Alabovsky et al.*, 1997; *Takenaka et al.*, 2003; *Erdmann et al.*, 2008; *Sarmadi and Ismail*, 2010).

The most studied hydrophilic antioxidants from meat are histidine-containing dipeptides, carnosine (ß-alanyl-L-histidine) and anserine (N-ß-alanyl-1-methyl-L-histidine), (*Decker et al.*, 2000; *Guiotto et al.*, 2005; *Arihara and Ohata*, 2006; *Di Bernardini et al.*, 2011; *Young et al.*, 2013). They are found only in meat, poultry and in some fish (*Young et al.*, 2013). The concentration of carnosine in meat depends on type of meat, and ranges from 500 mg/kg in chicken to 2700 mg/kg in pork, while anserine is present in higher amounts in chicken muscle (*Purchas and Busboom*, 2005; *Purchas et* *al.*, 2004; *Young et al.*, 2013). The antioxidant activity of these dipeptides is attributed mainly to their ability to chelate prooxidative metals such as copper, zinc and cobalt, but it has been found that carnosine is able to scavenge free radicals and form conjugates with potentially toxic aldehydic products from lipid oxidation as well (*Brown*, 1981; *Decker et al.*, 2000; *Young et al.*, 2013). It has been reported the ability of radioprotection of DNA by carnosine and anserine and protection of DNA by carnosine, against L-3, 4-dihydroxyphenylalanine Fe (III) induced damage. Some data showed that oral administration of L-carnosine has the same effect on increase of total antioxidant capacity of human serum as a consumption of beefsteaks (*Di Bernardini et al.*, 2011).

Apart from carnosine and anserine, there are many antioxidative peptides from meat sources, which are generated from proteins by different methods. In one study, *Saiga et al.* (2003b) treated porcine myofibrillar proteins with two proteases, papain and actinase E, and found that hydrolyzates derived in this way exhibit high levels of antioxidant activity in a linolenic acid peroxidation system. Compared to five isolated peptides from papain hydrolysate (DSGVT-actin, IEAEGE-unknown, DAQEKLE-tropomyosin, EELDNALN-tropomyosin, VPSIDDQEELM-myosin heavy chain) DAQEKLE showed the highest level of activity, which was very similar to the activity of a-tocopherol at pH 7. Also, it was reported that peptides which were obtained from myofibrillar proteins by actinase E treatment showed higher antioxidant activity, which proves that type of used proteolytic enzymes play an important role in determining the antioxidative properties of peptides (*Arihara and Ohata*, 2006; *Di Bernardini et al.*, 2011; *Ryan et al.*, 2011; *Udenigwe and Ashton*, 2013). In other study *Arihara et al*. (2005) found that peptides ALTA, SLTA, and VT, obtained from papain treated porcine skeletal muscle actomyosin exhibit antioxidative activity not only *in vitro*, but *in vivo* system, as well (*Arihara and Ohata*, 2006). Numerous studies were carried out on peptides derived from collagen (*Gómez-Guillén et al.*, 2011). *Li et al.* (2007) treated porcine collagen with pepsin and then derived hydrolysate was treated with papain, protease from bovine pancreas (PP) and a cocktail of three enzymes (PP, bacterial proteases from *Streptomyces* and *Bacillus polymyxa)*. The hydrolysate of collagen which was treated with cocktail of three enzymes showed the highest level of antioxidant activity, and four antioxidant peptides were isolated from this hydrolysate (QGAR, LQGM, LQGMH and HC) (*Li et al.*, 2007; *Di Bernardini et al.*, 2011; *Ryan et al.*, 2011). A 36-amino acid residue peptide GETGPAGPAGPIPVGARGPAGPQGPR GDKGETGEQ, which showed ability of free radical scavenging and metal chelating were isolated from bovine tendon collagen α1 by *Banerjee et al.* (2012), (*Udenigwe and Ashton*, 2013). Result of other studies showed that peptides obtained from papain-hydrolyzed beef sarcoplasmic proteins, and antihypertensive peptides from dry-cured ham also exhibited antioxidant activities (*Di Bernardini et al.*, 2012; *Escudero et al.*, 2012; *Udenigwe and Ashton*, 2013).

Anticancer properties

It has been proved that some peptides isolated from meat and marine organisms, especially fish, exhibit anti-cancer activity, inhibit cell proliferation and have cytotoxic effect against tumor cells (*Shahidi and Zhong*, 2008; *Ryan et al.*, 2011; *Najafian and Babji*, 2012; *Udenigwe and Aluko*, 2012).

Peptides with antibacterial activity isolated from beef sarcoplasmic proteins were investigated by *Jang et al.* (2008) in order to prove their cytotoxic effect against human breast adenocarcinoma (MCF-7), gastric adenocarcinoma (AGS) and lung carcinoma (A549) cell lines. GFHI showed the strongest cytotoxic effect on MCF-7 cells and decreased the cell viability of AGS cells. GLSDGEWQ strongly inhibited the proliferation of AGS cells, while none of tested peptides had a cytotoxic effect on A549 cells (*Jang et al.*, 2008; *Ryan et al.*, 2011; *Udenigwe and Ashton*, 2013). *Hsu et al*. (2011) isolated two peptides from tuna dark muscle which was treated with two proteases, papain and protease XXII. Amino acid sequences of these peptides were LPHVLTPEAGAT from papain hydrolysate and PTAEGVYMVT, from protease XXIII and both of them exhibited dose-dependent antiproliferative activities against human breast adenocarcinoma (MCF-7) cells, (*Hsu et al.*, 2011; *Ryan et al.*, 2011; *Udenigwe and Aluko*, 2012). *Picot et al.* (2006) reported 18 protein hydrolysates isolated from blue whiting, cod, plaice, and salmon to have antiproliferative activity against 2 human breast cancer cell lines (MCF-7/6 and MDA-MB-231) (*Picot et al.*, 2006; *Shahidi and Zhong*, 2008; *Ryan et al.*, 2011). In addition, it has be shown that hydrophobic peptide isolated from anchovy sauce, with molecular weight of 440.9 Da, induced apoptosis in a human lymphoma cell line (U937), (*Lee et al.*, 2003; *Lee et al.*, 2004; *Ryan et al.*, 2011).

These peptides, which showed to possess anticancer properties *in vivo*, could be further used to investigate their possibility to prevent the development of different types of cancer or even more, in their treatment.

Antibacterial properties

Antimicrobial peptides are usually composed of less than 50 amino acids, and about a half of them are hydrophobic (*Shahidi and Zhong*, 2008; *Najafian and Babji*, 2012). Their antibacterial activity is different and varies depending on origin of the peptides, amino acid composition, peptide size, charge, hydrophobicity, and secondary structure of peptides (*Shahidi and Zhong*, 2008). In recent number of years the overuse of antibiotics in human and veterinary medicine in order to reduce pathogens has led to phenomenon of multi-drug-resistance bacteria (*Sofos,* 2008; *Tohidpour et al*., 2010; *Bošković et al.*, 2013). One possible unconventional solution to this increasing problem could be the use of antimicrobial peptides in medical proposes (*Najafian and Babji*, 2012).

Antibacterial properties of peptides can be tested by several methods. The most commonly used method is agar diffusion. This method is based on measuring of the inhibition zone diameter formed on agar, but in order to determinate the exact antibacterial activity, the minimal inhibitory concentration (MIC) of peptides should be determined (*Di Bernardini et al.*, 2011; *Najafian and Babji*, 2012).

Although a number of peptides with antimicrobial activity have been isolated from milk proteins, there is no much data on the antimicrobial peptides from meat sources in the available literature (*Pihlanto*, 2002; *McCann et al.*, 2005; *Hayes et al.*, 2006; *McCann et al.*, 2006; *Minervini et al.*, 2003; *Di Bernardini et al.*, 2011; *Ryan et al.*, 2011; *Agyei and Danquah*, 2012).

In one study, *Jang et al.*, (2008) evaluated the antimicrobial effects of four peptides (GLSDGEWQ, GFHI, DFHING and FHG) isolated from beef sarcoplasmic proteins, which were previously determined to have ACE-I-inhibitory activity. Antimicrobial activity of these peptides was evaluated against three Gram- positive (*Bacillus cereus; Staphylococcus aureus* - KFRI00188; and *Listeria monocytogenes* -KFRI00719) and Gram- negative (*Salmonella typhimurium*-KFRI0025; *Escherichia coli*- ATCC43894 and *Pseudomonas aeruginosa*-KFRI00100) pathogenic bacteria. For this purpose the paper disc diffusion method was used, and peptides were applied at three different concentrations. All four tested peptides exhibited antimicrobial activities against one or more bacteria. Results showed that GLSDGEWQ had the highest level of antimicrobial activity, and was the only peptide that inhibited growth of both Gram-negative and Gram-positive bacteria at all three used concentrations. FHG inhibited *P. aeruginosa*, DFHING inhibited *E. coli* at all tested concentrations and GFHI exhibited antibacterial activity against *E. coli* and *P. aeruginosa*, but neither one of them inhibited the growth of *L. monocytogenes* (*Di Bernardini et al.*, 2011; *Ryan et al.*, 2011; *Udenigwe and Ashton*, 2013). Numbers of peptides with antimicrobial activity have been isolated from fish sources. *Liu et al.* (2008) isolated a cysteine rich antimicrobial peptide (CgPep33) from oyster muscle by using a combination of alcalase and bromelin. This peptide showed antimicrobial activity against pathogenic bacteria, such as *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*, and also some fungi (*Botrytis cinerea* and *Penicillium expansum*), (*Ryan et al.*, 2011). In a study conducted by *Gómez-Guillén et al.* (2010) it has been found that peptides obtained from tuna and squid skin gelatins showed high level of antimicrobial activity against *Lactobacillus acidophilus* and *Bifidobacterium animalis* subp. *lactis, Shewanella putrefaciens* and *Photobacterium phosphoreum* (*Gómez-Guillén et al.*, 2011). Protein from skin homogenate of *Epinephelus fario* by trypsin digestion, which showed activity against Gram-positive bacteria (*Vibrio alginolyticus, Vibrio parahaemolyticus, Vibrio fluvialis, Pasteurella multocida, E. coli, Aeromonas hydrophila* and *P. aeruginosa*) (*Najafian and Babji*, 2012).

Other properties

In recent years, obesity, hyperlipidemia and especially hypercholesterolemia became serious public health problems, which contribute mainly to cardiovascular diseases, but also to diabetes type 2, hypertension and stroke, certain forms of cancer and sleep-breathing disorder, as well. There is a great number of synthetic drugs with cholesterol-lowering effect, but nowadays researches are looking for natural alternatives which can be used in prevention and treatment of hypercholesterolemia (*Shahidi and Zhong*, 2008; *Ngo et al.*, 2012). One of such possibilities is the use of food derived peptides. Although mainly soy and milk derived proteins showed lipid-lowering effect, researchers investigate and explore other possibilities among other peptides derived from meat. One study showed that protein hydrolysate isolated from pork with papain exhibit a hypocholesterolemic effect in cholesterol-fed rats (*Morimatsu and Kimura*, 1992; *Morimatsu et al.*, 1996; *Shahidi and Zhong*, 2008).

There are some evidences that dipeptide carnosine exhibits significant pharmacological effects and could play a role in preventing or treating some pathological conditions, such as neurodegeneration, diabetes and cataract (*Guiotto et al.*, 2005; *Lee et al.*, 2005). These effects of carnosine were mainly related to its antioxidant or antiglycating properties (*Aldini et al.*, 2005; *Fu et al.*, 2009). *Baran* (2000) found that carnosine zinc complex alleviates injuries of gastric mucosa, acts against stomach ulcers and inhibits growth of the main gastric pathogen *Helicobacter pylori*. Some studies found that this antioxidative peptide also plays role in injury healing, recovery from fatigue and prevention of diseases related to stress (*Baran*, 2000; *Matsukura and Tanaka*, 2000; *Young et al.*, 2013). *Arihara et al.* (2005) isolated two peptides (ALTA and SLTA) from pork actomyosin by papain protease treatment. *In vitro* it has been found that these peptides showed antioxidative activity. In a study *in vivo* these peptides showed antifatigue effects after being orally applicated to mice which were running on treadmill (*Arihara and Ohata*, 2006).

In addition, it has been reported by *Nakatani et al*. (2009) that dipeptide PX isolated from porcine meat contributes to reparation and maintenance of cartilage by preventing mature chondrocytes from becoming mineralized and stimulating production of other protective peptides, while *Iwai et al.* (2005) found that peptides derived from collagen exhibit some immune-modulating activities by stimulating proliferation of fibroblasts, neutrophils, and monocytes (*Iwai et al.,* 2005; *Nakatani et al.*, 2009; *Udenigwe and Ashton*, 2013). Some peptides, such as commercial fish protein hydrolysate exhibits immunomodulatory activities by increasing the number of IgA+ cells and IL-4, IL-6 and IL-10 in the lamina propria of the small intestine in mice (*Duarte et al.*, 2006; *Möller et al.*, 2008).

Conclusion

Although, there is still a small number of studies, especially *in vivo* studies, which should be conducted in order to confirm safety and beneficial effects of bioactive peptides, scientific, technological and consumer interest for these peptides and their potential use in controlling and promoting health increases, and results remains to be seen.

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Bioaktivni peptidi iz mesa i njihov uticaj na zdravlje ljudi

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R e z i m e : Bioaktivni peptidi predstavljaju funkcionalne komponente unutar proteina i mogu se izolovati iz hrane biljnog i animalnog porekla, uključujući i meso. Nakon oslobađanja iz proteina tokom digestije u gastrointestinalnom traktu, ili nekom od metoda koje se koriste u proizvodnji hrane, ovi peptidi ispoljavaju različite biološke efekte i poseduju različite aktivnosti poput antioksidativne, antimikrobne, antihipertenzivne, antitrombotične, citomodulatorne i imunomodulatorne aktivnosti, a imaju ulogu i u snižavanju nivoa holesterola i borbi protiv kancera i gojaznosti. Aktivnost bioaktivnih peptida zavisi od njihove strukture, ali i drugih karakteristika. Uzimajući u obzir njihove biološke aktivnosti i pozitivan uticaj na ljudsko zdravlje, sa jedne strane, kao i milione smrtnih slučajeva uzrokovanih kancerom, kardiovaskularnim bolestima, kao i drugim bolestima povezanim sa načinom života, sa druge strane, očigledno je da ovi peptidi mogu naći primenu u unapređivanju ljudskog zdravlja i smanjenju rizika od pojave različitih oboljenja. Takođe, bioaktivni peptidi pokazuju određene prednosti u odnosu na sintetičke lekove.

Ključne reči: *funkcionalna hrana, ACE inhibitorni peptidi, proteini mišića, antioksidativne i antibakterijske osobine.*

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