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Food Derived Bioactive Peptides and its Application on Health Benefits

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Abstract

Bioactive peptides are specific sequences of amino acids, which are generated during food processing, microbial action, or enzymatic hydrolysis. Bioactive peptides have been researched for specific bio-functional role since many years. Well documented health benefits includes, antimicrobial activity, anticancer activity, anti-oxidative activity, antiaging activity, opioid activity, antithrombotic, hypocholesterolemic, immunomodulatory, cytomodulatory, mineral binding activity and also antihypertensive activity. Inhibiting mechanisms and structure of peptides plays crucial role in the bio-functional activity. Bioactive peptides with multi-functionality are now gaining special interest from researchers. Here, this article explained different functions of peptides, possible mechanisms of bioactive peptides, multifunctional role, and sources of multifunctional peptides.

Keywords: Bioactive peptides, multifunctional role, proteins

Proteins have important functions in living body systems and also reduce risk of chronic diseases (Parvez *et al.* 2006). Korhonen (2009) defined food proteins or food proteins hydrolysates, as compounds which were reported to provide rapidity to "hormone-like" activities *in vitro* and/or *in vivo.* Bioactive peptides are some specific protein sequences of amino acids, which provides measurable biological health effects and influence body positively, upon ingestion and absorption of it (Korhonen and Pihlanto, 2006). Bioactive peptides usually contain 2–20 amino acid residues (Wijesekara and Kim, 2010). Bioactive peptides have different bio-functional properties like Antihypertensive, antioxidant, antithrombotic, opioids and many other (Yang *et al.* 2009).

Well characterized sources of bioactive peptides

Bioactive peptides have been derived, isolated, and characterized from different food proteins. It includes, plants, animals and marine food proteins, like milk, cheese, rice, wheat, soy, beef, sea weed, Spirulina, fish etc (Agyei *et al.* 2015). Wide range of food products and natural foods were tested for the determination of bioactive peptides and their bio-functional properties. Milk and milk products includes, caseins, and whey proteins based bioactive peptides (Nielsen *et al.* 2017). From plant proteins, soy, maize, rice, and wheat etc were determined as a sources of bioactive peptides. In case of animal proteins, proteins from bovine, chicken and porcine muscle, reported as a sources of different bioactive peptides. Also, from marine sources, fish proteins from bonito, sardine, tuna and salmon were determined as a sources of bioactive peptides. (Vercruysse *et al.* 2005).

Strategies for the production of bioactive peptides

Bioactive peptides can be produced through following ways: (a) Enzymatic hydrolysis *in vitro* or *In vivo* (b) Food processing (c) Microbial fermentation

(Danquah and Agyei, 2012). Also, the production of bioactive peptides was reported in the human gut (Korhonen and Pihlanto, 2006; Dziuba and Dziuba, 2014). Synthesis of bioactive peptides is also possible after recognizing the specifics sequence of amino acids of peptides. Three pathways are reported for this: (1) recombinant DNA technology, (2) enzymatic synthesis; and (3) chemical synthesis (Korhonen and Pihlanto 2003).

Enzymatic hydrolysis

Enzymes like pepsin, trypsin or chymotrypsin, are responsible for protein hydrolysis in the gastrointestinal digestion (Korhonen and Pihlanto, 2003). Various bioactive peptides have been reported to be released from milk and milk proteins upon the enzymatic action pepsin, trypsin and chymotrypsin enzymes (Gobbetti *et al.* 2007) and other enyzymes like thermolysin, alcalase and subtilisin also used to produce bioactive peptides (Korhonen, 2009). Commercial proteolytic enzymes like Alcalase®, papain, Neutrase®, thermolysin, Flavourzyme®, and Actinase E® are also used for the generation of bioactive peptides from meat at industrial scale (Mora *et al.* 2014).

Food processing

Bioactive peptides produced during food processing and storage of products. Some researchers also reported the generation of bioactive peptides due to the action of plasmin (present in milk), which hydrolyses the milk proteins and produce bioactive peptides (Dalsgaard *et al.* 2008). Endogenous muscle peptidases produced peptides after several months of ripening in meat products like dry cured ham (Mora *et al.* 2014).

Microbial fermentation

Proteolytic activity of various starter cultures and non-starter bacteria is reported as a method used for the generation of bioactive peptides from various dairy and food products. Lactic cultures were reported to generate bioactive peptides through their proteinases and peptidases (Christensen *et al.* 1999; Williams *et al.* 2002; Manzanares *et al.* 2015). Microbial fermentation is a common method used worldwide for the generation of bioactive peptides in the fermented milks like yoghurt, whey, cheese, and other milks (Korhonen and Pihlanto, 2003). Solanki *et al.* (2017); Solanki and Hati (2018), isolated and characterized the Angiotensin-I converting enzyme (ACE) inhibitory peptides from camel milk fermented by *Lactobacillus fermentum* TDS030603 (LBF) and *Lactobacillus bulgaricus* NCDC (09), and *Lactobacillus rhamnosus* under specific optimized growth conditions. Hati *et al*. (2015) used milk fermented with *Lactobacilli* isolates to study ACE-inhibitory and antimicrobial activity.

Possible mechanisms of actions of bioactive peptides

Antihypertensive peptides

Hypertension is a most common risk factor in the development of cardiovascular diseases (Murray and FitzGerald, 2007). Primary sequences of caseins, whey proteins, meat and other food proteins are the sources of peptides, derived through enzymatic/ bacterial hydrolysis (Murray and FitzGerald, 2007). Mainly two enzyme based systems such as Kinin-nitric oxide system (KNOS) and Renin-angiotensin system (RAS), including different metabolic routs are responsible for high blood pressure (Martínez-Maqueda *et al.* 2012).

ACE-inhibitory peptides

In the RAS the conversion of angiotensinogen to angiotensin II (Vasocostrictory peptide) is catalyzed by Renin and ACE during intermediate steps. Thus, inhibition of ACE consequentially leads to blood pressure reduction (FitzGerald *et al.* 2004). ACE-inhibitory peptides are derived from many plants, animal sources. In the KNOS, ACE enzyme comprehensively inactivates the natural vasodilators (Kallidin and bradykinin). Binding action of Bradykinin, it binds to β-receptors and stimulation of nitric oxide synthase (NOS) produces vasodilation (FitzGerald *et al.* 2004). Recently, Feeney *et al.* (2017), had identified and characterized nine different ACE-inhibitory peptides such as PFL, FFG, WWK, FFFL, FPIL, WCY, FEPL, FLLA, CPA, from food proteins and tested their inhibitory activity with Captopril®. Their study revealed that, at the concentration of 1 mg protein/mL, peptides showed 96.5% ACE-inhibition in *in vitro* assay.

Renin Inhibitory peptides

Renin inhibition prevents the formation of potent vasoconstrictor (Ang- II) (Staessen *et al.,* 2006). Renin inhibitory peptides are more specific (Staessen *et al.* 2006; Udenigwe *et al.* 2011). Pea protein derived peptides exhibited rennin inhibitory activity (Li and Aluko, 2010).

Opioid-Induced blood pressure regulation

Opioid peptides are reported to work as a blood pressure regulating agents. Their binding with receptors reported to induce effects like morphine. These receptors also take part in the regulation of blood circulation in the body and blood pressure regulation. Wheat gluten, casein, and rapeseeds etc were identified as a source of opioid peptides (Jauhiainen and Korpela, 2007). Nurmien *et al.* (2000) reported the antihypertensive effects of an opioid peptide α-lactorphin (Tyr-Gly-Leu-Phe) on normotensive Wistar Kyoto rats (WKY) and spontaneously hypertensive rat (SHR) *in vivo.*

Endothelin converting enzyme (ECE) and Endothelin-1 inhibitory peptides

In this mechanism, Endothelin-converting enzyme (ECE) present in the body releases the vasoconstrictory peptide endothelin-1 (ET-1) from big endothelin-1 (big ET- 1). Furthermore, the vasoconstriction is observed due to the two receptors (ETa and ETb) of ET-1 (FitzGerald *et al.,* 2004). Egg protein derived peptide ovokinin (f 2-7) shows Endothelial-dependent release of NOS, as the mechanism for antihypertensive effect (Matoba *et al*., 1999). Ovokinin (f 2–7) also modulates a hypotensive activity (Scruggs *et al.,* 2004). Okitsu *et al*. (1995) found ECE inhibitory peptides from beef and bonito pyrolic appendix. Bovine β-lactoglobulin based peptide Ala-Leu-Pro-Met-His-Ile-Arg inhibited the release of ET-1 in cultured porcine aortic endothelial cells (PAECs) (Maes *et al.* 2004).

Antimicrobial peptides

Nowadays, antimicrobial peptides (AMPs) are known as an important first line of protection against pathogens (Mulero *et al.* 2008). AMPs are small peptides (from 12 to 80 amino acids), low molecular weight (from 1 to 5 kDa) and mostly found as cationic and amphipathic (Brogden *et al.* 2003). AMPs play an important function in inflammation and its modulation in innate immune system (Cuesta *et al.* 2008). AMPs modulate the adaptive response (Oppenheim *et al.* 2003), acts as chemokines to recruit other effect or cells (Chertov *et al*. 1996), and also AMPs are promising candidates as potential therapeutic molecules (Bridle *et al.* 2011). From the many report, it was found that, antimicrobial peptides showed these mechanisms 1) penetration and disruption of microbial membrane integrity or 2) translocation across the membrane and actions on internal targets (Steinstraesser *et al.* 2011). Many antimicrobial peptides isolated from milk proteins (Demers *et al.* 2013), and soy proteins (Vasconcellos *et al.* 2014) and egg protein (Zambrowicz *et al.* 2014).

Antidiabetic peptides

Obesity is a risk factor for several medical problems. Overweight places extra stress on body, including maintaining blood sugar levels leads to diabetes. Aglycin, natural antidiabetic peptide from soy bean (Dun *et al.* 2007), showed antidiabetic effects in mice with diabetes (Lu *et al.* 2012). Yang *et al.* (2012) reported the anti-diabetic action of meju (unsalted fermented soybeans). Inhibition of Dipeptidyl peptidase IV enzyme with KA and AAATP peptides from dry-cured ham showed antidiabetic effect (Mora *et al.* 2015).

Anti-oxidative peptides

Oxidative stress advertently triggers certain CVD as well as inflammatory diseases (Ramalingam and Kim, 2012). Bioactive peptides show anti-oxidative activity through various mechanisms (Aluko, 2012). Hydrolyzed soybean (Park *et al*. 2010), milk proteins (Rival *et al.* 2001), sweet potato (Zhang *et al.* 2012), meat proteins (Mora *et al.* 2014) and eggs (Aluko, 2012) were identified as a potential sources of anti-oxidative peptides.

Anticancer peptides

Cancer is a global health burden; may be controlled by nutritional supplements and diet (Uster *et al.* 2013). Food proteins and peptides are reported to work as a checking agent in the different stages of cancer, like promotion, progression and initiation (De-Mejia and Dia, 2010). Anticancer peptides are derived from milk proteins (caseins), soy proteins (Lunasin) and many marine organisms (Roy *et al.* 1999; Otani and Suzuki, 2003; Kim *et al.* 2000; Kim *et al.* 2012). Bioactive peptides showed protective effects in cancer development by regulating the cell viability and immune cell functioning (Meisel, 2005).

Opioid peptides

Opioid peptides possess some form of affinity for opiate receptors and can exert effects on the nervous system and GI functions. Naturally occurring opioid peptides in the body (usually brain and pituitary gland) are called endorphins and enkephalins while opioid peptides obtained from enzymatic digests of food proteins are called exorphins. Opioid peptides categorized as opioid agonists and antagonists with different functions (Aluko, 2012). Many milk casein based opioid agonist peptides were reported like, β-Casomorphins (Rokka, 1997), Whey protein-derived peptides like *α*-lactorphin and *β*-lactorphin (Pihlanto, 2001), while opioid antagonists (casoxins) were derived from bovine *k*-casein (Yoshikawa, 1994).

Antithrombotic peptides

Thrombosis is a local coagulation of blood in the circulatory system, leads to CVD (Grundy *et al.* 1998). Antithrombotic peptides inhibit blood clotting and may be used to treat thrombosis. Bovine k-casein and human lactoferrin has been shown to inhibit thrombosis (Jolles *et al.* 1986; Mazoyer *et al.* 1990; Fosset, 2000).

Hypocholesterolemic peptides

Hypercholesterolemia is positively linked with the likelihood for the development of CVD (Grundy *et al.* 1998). Many food proteins/peptides are known for their cholesterol-reducing effect (e.g., pork protein hydrolysate, milk β-lactoglobulin hydrolysate, soy 7S globulin, soy protein hydrolysate, and soy glycinin fragment,). Soybean is the most known and well recognized source for the hypocholesterolemic peptides. Two different mechanisms are observed for the two different sources of proteins (i.e., Soybean, and whey proteins) (Bhat *et al.* 2015). In case of soybean protein/peptides, the cholesterol lowering effect found to be correlated with the bile-acid-binding capacity of the soybean proteins/peptides (Making *et al.* 1988). While in case of whey proteins/peptides, these proteins reported to affect the cholesterol absorption and the serum cholesterol level. Also reported to controls the intestinal emulsification and the nature of the resulting micelles (Nagaoka *et al.* 2001).

Immunomodulatory peptides

Immunomodulatory peptides can enhance immune cell functions (Horiguchi *et al.,* 2005). These functions includes, antibody synthesis, lymphocyte proliferation, cytokine regulations and natural killer (NK) cell activity (Horiguchi *et al.* 2005). Immunomodulatory peptides are reported to decrease allergic reactions and raise mucosal immunity in the GI tract (Korhonen and Pihlanto, 2003). Immunomodulatory peptides trigger non-specific defense system (Kitts and Weiler, 2003). Thee peptides are derived from tryptic hydrolysates of rice, milk and soy proteins (Korhonen and Pihlanto, 2003).

Cytomodulatory peptides

Cytomodulatory peptides derived from different food proteins regulate viability (e.g. apoptosis, differentiation, and proliferation) of body cells. Milk based peptides are reported to trigger apoptosis of cells. Combined actions of these immunomodulatory and cytomodulatory activities may give to defensive activity in tumor growth (Meisel and FitzGerald, 2003).

Mineral binding peptides

Mineral binding peptides are derived from milk casein and egg having activity like anti-cariogenic. Peptides are composed of serine-phosphate residues. Casein based phosphorylated peptides were reported to build soluble organophosphate salt and ultimately leads to increase mineral uptake. This results in increased recalcification of enamel (Meisel, 1998). Structural features of each peptides vary in specific amino acid sequence, based on which peptides show different biological activity (Erdmann *et al.* 2008).

Multifunctional food peptides

Several protein hydrolysates and peptides have been identified to possess more than one physiological attributes and are called multifunctional peptides. Biological effects of peptides in one area in the human body system, affect positively to the other area. According to Sistla (2013), multifunctionality of bioactive peptides is concerns with various functions which includes, immunomodulation, ACE-inhibitory, opioid or mineral binding and cytomodulatory activities which are combined with the other functions of the same peptide.

Milk based multifunctional peptides and proteins

Lactoferrin and its derivatives

Lactoferrin (LF) is a multifunctional protein of transferrin family, and also known as metal-binding protein (Levay and Viljoen, 1995). LF is reported to control the availability of iron for the immune system modulation. LF showed diverse functionalities (Korhonen and Marnila, 2013). The LF hydrolysate (lactoferricin), a peptide has been exhibited antitumor, antimicrobial and anticancer properties (Theolier *et al.* 2013). LF hydrolysate has shown versatile biological roles (Cornish *et al.* 2007).

Casein-based phosphopeptides from milk

Hydroltic action of pepsin on milk generate casein phosphopeptides (CPPs) (Clare and Swaisgood, 2000). Multifunctional functions of CPP include anticariogenic, antihypertensive properties, immune enhancing effects, and cytomodulatory effects (Fan *et al.,* 2013). CPPs have been reported as anticariogenic, ability to stabilize amorphous calcium phosphate (ACP) (Walker *et al.* 2009). CPPs provide calcium and other minerals (manganese, zinc, iron, and copper) in the intestine in a highly bioavailable form (at intestinal pH) (Aluko, 2012). CPPs have been reported with some other health beneficial effects based on their mineral solubilization properties (Korhonen and Pihlanto, 2006). Studies on albino mice and *Catlacatla* revealed CPPs as an antigenotoxic agent. It can be used for the making of formulations which are required for the workers who are exposed to low levels of radiation to prevent from occupational hazard (Balaji and Arunachalam, 2011). CPPs have potential to be used as an anticancer agent (Arunachalam *et al.* 2012). Many other milk-derived peptides reveal multifunctional properties derived from caseins and whey proteins (Meisel, 2004).

Glycomacropeptide (GMP)

GMP, is a glycopeptide f(106-169) generated from the κ - casein protein upon the enzymatic action. Various physiological functions attributed to GMP such as inhibition of binding of *Cholera* toxin (CT) to Chinese hamster ovary (CHO)-K1 cells and ganglioside G_{M1} (Kawasaki *et al.* 1992) inhibition of bacterial adhesion (Nakajima *et al.* 2005); suppression of gastric secretions (Beucher *et al.* 1994); promotion of bifidobacterial growth (Janer *et al.*, 2004); immunosuppressive effect (Otani *et al.* 1992); regulation of blood circulation through antihypertensive (Manso and Lopez-Fandino, 2003) and antithrombotic activity (Jolles *et al.* 1986).

Egg-derived multifunctional peptides

Egg is a rich source of multifunctional bioactive peptides, it includes Lysozyme peptides (Mine *et al.* 2004 ; You *et al.* 2010), Lipovitellenin peptide (Abdou *et al.* 2013), Ovoalbumin peptide (Ovokinin) (Davalos *et al.* 2004), Phosvitin peptides (Zambrowicz *et al.*

2014), Egg yolk bone peptides (Bonepep®) (Leem *et al.* 2004; Oi *et al.* 2005), Egg white peptides (Runpep®) (El-Mahmoudy *et al.* 2005).

Plant protein-derived multifunctional peptides

Plant protein derived multifunctional bioactive peptides includes Limenin (Wong and Ng, 2006); Rapakinin (Yamada *et al.* 2010; Yamada *et al.* 2011); Rubisco-derived peptides (Zhao *et al.* 2008); Soymorphin (Yamada *et al.* 2012; Kaneko *et al.* 2010); Zein (Miyoshi *et al.* 1995); Lunasin (Galvez and de Lumen, 1999; Seber *et al.* 2012).

Role of bioactive peptides in pharmaceuticals

Bioactive peptides serve as nutraceuticals and functional foods (Hajirostamloo, 2010), important role as pharmaceuticals (Lax, 2012; Siniscalco and Antonucci, 2013), also influence as skin care in dermopharmaceutical products (Fields *et al.* 2009; Lintner, 2000; Zhang *et al.* 2011).

Application of bioactive peptides on clinical studies

Large proportion of human studies found on antihypertensive activities as compared to other activities like antioxidant, anticancer etc (Agyei and Danquah, 2012). For proposing health benefits it is must to find out dosage amount and states. Health function proposed through many of screening methods and series of experiments (Hartmann and Meisel, 2007). Some human studies performed by (Mizushima *et al.* 2004; Mizuno *et al*. 2005; Aihara *et al*. 2005; Walker *et al.* 2009) to check the bio-functionality of bioactive peptides. Multifunctional peptides have been proposed as less allergenic agents as compared to their native proteins (Host and Halken, 2004).

CONCLUSION

Scientists working in food science, are taking keen interest to exploit novel bioactive peptides from the byproducts or other unconventional sources from agriculture wastes to establish their possible functions and health benefits. In food industries, peptides rich Calpis and Evolus are the two well established fermented milks available in the market with a valid heath claims. However, peptides rich foods with specific health benefit is available only in few developed countries in the world. Under such context, characterization and quantification of peptides for particular health claim need to be studied before approving a product as a functional food with specific health claims.

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