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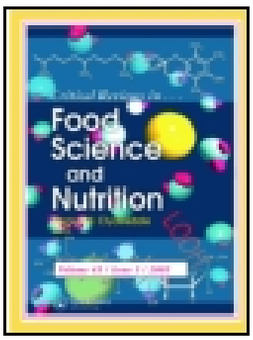

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Peptides: Production, bioactivity, functionality, and applications

Mona Hajfathalian[a], Sakhi Ghelichi[a,b], Pedro J. García-Moreno[a], Ann-Dorit Moltke Sørensen[a], and Charlotte Jacobsen[a]

[a]Division of Food Technology, National Food Institute, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark; [b]Department of Seafood Science and Technology, Faculty of Fisheries and Environmental Science, Gorgan University of Agricultural Sciences and Natural Resources, Gorgan, Iran

ABSTRACT

Production of peptides with various effects from proteins of different sources continues to receive academic attention. Researchers of different disciplines are putting increasing efforts to produce bioactive and functional peptides from different sources such as plants, animals, and food industry by-products. The aim of this review is to introduce production methods of hydrolysates and peptides and provide a comprehensive overview of their bioactivity in terms of their effects on immune, cardiovascular, nervous, and gastrointestinal systems. Moreover, functional and antioxidant properties of hydrolysates and isolated peptides are reviewed. Finally, industrial and commercial applications of bioactive peptides including their use in nutrition and production of pharmaceuticals and nutraceuticals are discussed.

KEYWORDS

Peptides; hydrolysate; bioactivity; functional properties; antioxidant properties; application

Introduction

Dietary protein is an important source of energy (4 kcal/g protein) and essential amino acids, which are needed for growth and maintenance of physiological functions such as repair of tissues and cell signaling. In the body, proteins are broken down to peptides upon digestion by endogenous enzymes in the gastrointestinal system. These peptides are inactive within the sequence of the parent protein, but after they are released by enzymatic hydrolysis, they exert various physiological functions. Recent research has shown that peptides from different sources such as dairy products, plants, animals and seafood have a wide range of bioactivities, e.g., antimicrobial (Tang et al., 2015), immunomodulatory (Mechkarska et al., 2014), antihypertensive (Capriotti et al., 2015), and antioxidant (Babini et al., 2017) activities, among others.

Bioactive peptides can also be produced by commercial exogenous enzymes, which hydrolyze proteins into peptides. The greatest number of bioactive peptides isolated to date is from milk proteins. Other sources include meat, fish, eggs, plant sources such as soy and wheat (Hartmann and Meisel, 2007). The most commonly used enzymes for the production of bioactive peptides, for instance, from fish proteins include Alcalase 2.4 L FG, Papain, Pepsin, Trypsin, α-chymotrypsin, Pancreatin, Flavourzyme, Pronase, Neutrase, Protamex, Bromelain, Cryotin F, Protease N, Protease A, Orientase, Thermolysin, and Validase (Raghavan and Kristinsson, 2008; Ren et al., 2008; Samaranayaka and Li-chan, 2008; Je et al., 2009; Hsu, 2010; Ngo et al., 2010). Some of these enzymes are also used for production of bioactive peptides from other sources.

A large proportion of the global production of dietary proteins is being discarded as waste or sold at a low price for animal feed after the main products have been produced from the original raw material. For example, rapeseed meal with a low solubility is produced as a by-product from the production of rapeseed oil (Tan et al., 2011). Likewise, head, bones, tails and intestines are by-products from the seafood production, which currently provide the manufacturer with low or no revenue. Therefore, it seems crucial to find avenues toward making the best use of such protein sources, for example by using them for the production of protein hydrolysates containing bioactive peptides for human consumption (Sila and Bougatef, 2016). One of the challenges associated with this strategy is the removal of bitterness from such peptide formulations because the bitterness negatively affects consumer perception (Zhao et al., 2015).

Protein hydrolysates and peptides from natural resources can be used as "functional foods" and "nutraceuticals" on the basis of their bioactivity, or as technological components thanks to their functional properties. The functional products and nutraceuticals may contain the whole hydrolysate and/or isolated and purified peptides (Lafarga et al., 2016). Since the bioactivity and functionality of peptides depend on their amino acid composition, sequence, and molecular mass (Lassoued et al., 2015a), peptides with varying effects might be derived from a single hydrolysate. Therefore, sometimes additional stages of isolation and purification are required in order to incorporate peptide(s) with intended effect(s) in the final product. This isolation process is predominantly carried out by controlling the process of enzymolysis (Zou et al., 2016).

This review aims to provide an overview of state-of-the-art technologies for the production and purification of protein hydrolysates including technologies for the removal of bitterness. A second aim is to provide a comprehensive overview of the activities that have been reported for protein hydrolysates from various protein sources such as dairy, egg, animal, fish, and plants. The review will cover bioactivities with a potential

CONTACT Charlotte Jacobsen chja@food.dtu.dk; www.food.dtu.dk Professor mso and group leader Research group for Bioactives - Analysis and Application Division of Food Technology DTU Food Technical University of Denmark National Food Institute Kemitorvet Building 204, room 112 2800 Kgs, Lyngby, Denmark.

impact on human health including effects on the immune, cardiovascular, nervous and gastrointestinal systems. Functional properties of protein hydrolysates such as emulsifying, water binding, and antioxidant properties in foods will also be discussed. A final aim of the review is to critically assess potential applications of protein hydrolysates/bioactive peptides in pharmaceutical, sports nutrition, food and feed applications on the basis of the current knowledge and documentation of their bioactivity.

Production of bioactive and functional peptides

In order to exhibit their beneficial effects on health, bioactive peptides must be released from the primary structure of food proteins, where they remain bonded to other amino acids. Moreover, protein hydrolysis can also lead to hydrolysates with improved techno-functional properties (e.g., solubility, emulsifying, foaming, oil and water binding, and gelling) (Wouters et al., 2016). The release of bioactive peptides is achieved by degrading the original proteins by using chemicals (e.g., acids and alkalis) or enzymes. Proteolysis caused by enzymes is preferred to chemical hydrolysis since: (i) the reaction is carried out at mild conditions of pH (e.g., 4–8) and temperature (e.g., 40–60°C), (ii) side reactions are avoided because of the high specificity of the enzymes, and (iii) the peptides obtained maintain their nutritional value (Guerard, 2006). Therefore, this review focuses on the production of bioactive peptides by enzymatic hydrolysis, including fermentation where enzymes are secreted by the microorganism(s) taking part in the process. Technologies for removal of bitterness are also discussed. In addition, the fractionation, purification and identification of bioactive peptides, including bioinformatics-driven approaches, are covered in this section.

Enzymatic protein hydrolysis

Enzymatic hydrolysis of proteins is catalyzed by proteases, which cleave peptide bonds between two amino acids consuming a molecule of water per bond cleaved (Eq. 1). Hence, the continuous cleavage of peptide bonds breaks down proteins into products of lower molecular weight such as peptones, peptides, and amino acids (Adler-Nissen, 1986).

$$P1 - CO - NH - P2 \rightarrow P1 - COOH + P2 - NH_2 \quad (1)$$

Independently of the type of food protein, the enzymatic hydrolysis process commonly comprises the following stages (Fig. 1): grinding the raw material and homogenization in water (or buffer), temperature equilibration and pH adjustment to the optimum values of the enzyme employed, followed by enzyme addition (García-Moreno et al., 2010). Recently, ultrasonic-assisted hydrolysis was evaluated with the purpose of facilitating the production of low molecular weight peptides (Kadam et al., 2015). Upon completion of the reaction, the enzyme needs to be inactivated by heating or pH adjustment. Alternatively, continuous membrane reactor, where the enzyme is continuously recycled to the reaction tank, might also be used in order to stop the reaction and save enzyme costs (Prieto et al., 2010a). Subsequently, the digested material, which contains the bioactive peptides, is separated from the precipitate and lipids (e.g., centrifugation/decantation), fractionated, and further stabilized (e.g., by spray-drying) (Abdul-Hamid et al., 2002; Espejo-Carpio et al., 2014a).

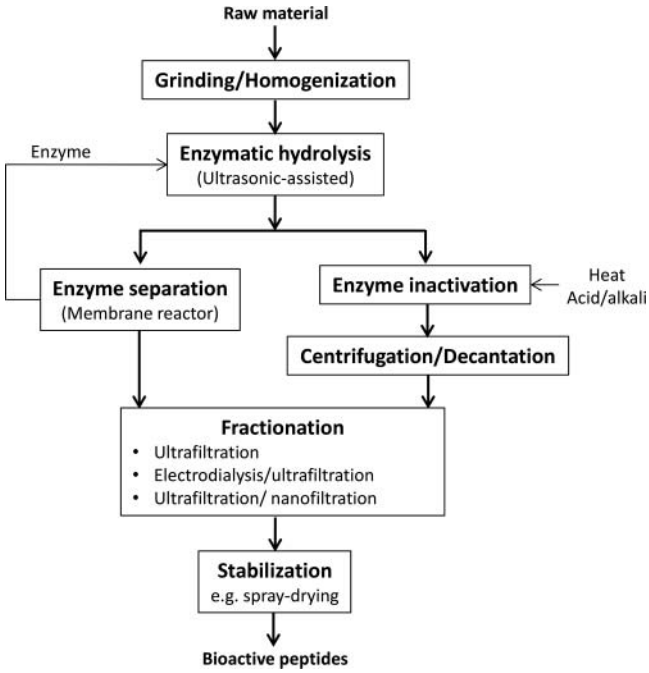

Figure 1. Flow diagram for the production of bioactive peptides.

Employing a proper enzyme and having good control over processing conditions (e.g., pH, temperature, enzyme/protein ratio, and time) are critical aspects for the production of protein hydrolysates with the required properties (Kristinsson, 2006). Indeed, these process variables determine the extent of the hydrolysis reaction for a protein–enzyme system. This is normally indicated by the degree of hydrolysis (DH), which is defined as the percentage of peptide bonds cleaved. There are several methods to determine the DH such as pH-stat, trinitrobenzenesulfonic acid (TNBS), o-phthaldialdehyde (OPA), trichloroacetic acid soluble nitrogen (SN-TCA), and formol titration methods. Among them, the pH-stat method is the most commonly employed since it allows maintaining the pH constant at the optimum of the enzyme and measuring the DH in real time (Rutherfurd, 2010). However, because this method is based on the titration of the proton released or consumed after the cleavage of the peptide bond, it is only suitable when the reaction is carried out under alkaline (>7.5–7.8) or acidic (<3.1–3.6) pH, respectively (Adler-Nissen, 1986). Another drawback of this method is the high salt content of the final hydrolysate as a consequence of the alkali or acid addition, which is required to maintain the pH constant and monitor the DH (Whitehurst and van Oort, 2009). As suggested by a recent study on whey protein, an interesting alternative could be to carry out the hydrolysis reaction without controlling pH (Le Maux et al., 2016). This work indicated that the bioactive properties of the hydrolysates (e.g., antioxidant and antidiabetic) might or might not be influenced by the control of the pH, depending on the enzyme employed (e.g., papain or a microbial-derived alternative).

In the enzymatic hydrolysis process, the specificity of the enzyme used is particularly important. This is because it affects size, amount, amino acid composition and amino acid sequence of the peptides produced, which in turn influences the bioactive and functional properties of the hydrolysates (Sarmadi and Ismail, 2010). Although crude proteases extracts (e.g., from fish) have been successfully used as catalysts in enzymatic hydrolysis (Bougatef et al., 2010; Lassoued et al., 2015b), commercially purified enzymes are preferably employed since they allow a better control over the hydrolysis process (e.g., shorter reaction time for a desired DH, more consistent peptides size and composition) (Samaranayaka and Li-Chan, 2011). Consequently, industrial proteases derived from different sources such as microorganisms (e.g., Alcalase, Neutrase, Protease P "Amano" 6, Flavourzyme, Protamex) (Halldorsdottir et al., 2013; Venuste et al., 2013), animals (e.g., PTN, pepsin, trypsin, α-chymotrypsin, pancreatin) (Wu et al., 2015a, b; García-Moreno et al., 2017) and plants (e.g., papain, bromelain) (Salampessy et al., 2015; Elavarasan et al., 2016) have been widely employed for the production of protein hydrolysates exhibiting bioactive and/or functional properties. These marketable proteases may mainly contain endopeptidases (e.g., trypsin, subtilisin, papain), or a combination of endopeptidases and exopeptidases (e.g., carboxypeptidases, aminopeptidases). Additionally, several enzymes can be utilized in the production of only one protein hydrolysate. Although they may be added simultaneously (Yamada et al., 2013; García-Moreno et al., 2017), sequential addition (e.g., after progressive decrease in the reaction rate) is normally carried out in order to achieve hydrolysates with a higher DH (Vaštag et al., 2011; García-Moreno et al., 2014, 2015).

Fermentation

In addition to proteolysis through chemical digestion and/or addition of commercial enzymes to substrate, certain microbial strains secreting proteases can also be used to hydrolyze protein-rich substrates. The released peptides can have a high level of bioactivity with health-related benefits and better functional properties (Elfahri et al., 2016; Sanjukta and Rai, 2016; Rai et al., 2016).

The higher bioactivity of peptides from fermented products compared to the raw materials could be attributed to the change in amino acid composition in addition to size and sequence of the peptides. Xu et al. (2015) reported that the amounts of essential amino acids increased greatly following fermentation of soybean. Kleekayai et al. (2015) identified two ACE-inhibitory peptides (SV and IF) and one antioxidant peptide (WP) from fermented shrimp pastes. Pan et al. (2005) obtained two antihypertensive peptides with amino acid sequences of VPP and IPP from skimmed milk hydrolysate digested by cell-free extract of *Lactobacillus helveticus*. They proposed that the amino acid composition of the peptides accounts for bioactive effects of the fermented products.

Lactobacillus spp. is one of the most widely used genera for fermentation of protein-rich resources to release bioactive peptides. Upon the use of *Lactobacillus*, the foodstuff rapidly becomes acidified due to the production of lactic acid (Vallabha and Tiku, 2014). Production of lactic acid, which is an organic acid, may elongate the shelf life and render microbial safety and sensory quality to the final product (De Vuyst and Leroy, 2007). Besides, *Lactobacillus* can influence polypeptide quality by controlling cellular proteolysis. This is presumably done by degradation of protein into oligopeptides through their cell-envelope proteinase; cells absorb the oligopeptides via their peptide transport systems and transform them into shorter peptides and/or amino acids by intracellular peptidases (Savijoki et al., 2006). Lactic fermentation is useful not merely to attain bioactive peptides, but also to recover other components such as chitins, lipids, and minerals (López-Cervantes et al., 2006). Fermentation by lactic acid bacteria may also enhance organoleptic properties of final products (Aguirre et al., 2014). The efficiency of lactic acid bacteria in production of bioactive peptides can be related to their elaborate proteolytic system. It consists of a cell envelope proteinase, which initializes protein degradation, a transport system, and many intracellular peptidases (Pescuma et al., 2015).

Lactic fermentation has been adopted to attain bioactive peptides from milk resources such as antioxidant peptides from camel milk (El Hatmi et al., 2016), antioxidant, ACE inhibitory, antimicrobial, and immunomodulating peptides from whey β-lactoglobulin (Pescuma et al., 2015), and antimutagenic and anti-inflammatory peptides from β-casein (Espeche Turbay et al., 2012). In addition, Amadou et al. (2011) performed fractionation on the fermented soy protein meal hydrolysate by *Lactobacillus plantarum* and found that some fractions had great antioxidant activities. Jain and Kumar Anal (2017) produced functional and bioactive protein hydrolysates through fermentation of chicken eggshell membrane by using *Lactobacillus plantarum*. The resulting hydrolysates exhibited favorable functional properties with respect to solubility, foaming capacity, and emulsification activity as well as bioactivity in terms of DPPH-radical scavenging, reducing power, angiotensin-I converting enzyme inhibition, and protection against foodborne pathogens. Furthermore, Mechmeche et al. (2017) reported the production of bioactive peptides with antioxidant activity by using the fermentative strain *Lactobacillus plantarum* and tomato seed meal extract as the substrate.

Fermentation of protein resources have also been performed by using other genera of fermenting bacteria. Meinlschmidt et al. (2016) studied fermentation of soy protein isolate by *Bacillus* spp., *Rhizopus* spp., and *Saccharomyces* spp. in addition to *Lactobacillus* spp. and found that all fermented products were more soluble and had less off-flavor than nonfermented protein isolate. Moreover, Jemil et al. (2016) obtained antioxidant and ACE-inhibitory peptides (NVPVYEGY, ITALAPSTM, SLEAQAEKY, and GTEDELDKY) from sardinelle protein hydrolysates fermented by two species of *Bacillus* spp. namely *B. subtilis* and *B. amyloliquefaciens*. Furthermore, Jemil et al. (2014) prepared protein hydrolysate from sardinelle, zebra blenny, goby, and ray via fermentation by *Bacillus subtilis* and found that the hydrolysate had antioxidant and antimicrobial effects. Zhao et al. (2016a, b) produced protein hydrolysate from surimi through fermentation by *Actinomucor elegans*; they stated that the end product had a higher sensory acceptability compared to surimi before fermentation. Kumar Rai et al. (2017) produced protein hydrolysates rich in bioactive polyphenols by using three fermentative strains from Bacillus

spp. namely *B. subtilis* KN12C, *B. amyloliquefaciens* KN2G, and *B. licheniformis* KN13C. They claimed that these strains possessed high protease, α-amylase and β-glucosidase activities.

On the whole, fermentation is a promising method in order to prepare bioactive peptides from protein resources, especially those with limited consumption and/or from discarded sources. *Lactobacillus* spp. is the most prevalent genus to obtain bioactive peptides via fermentation although other genera such as *Bacillus* spp. are also used. Fermentation is prioritized over acid/base digestion since it does not cause the loss of essential amino acid and environmental pollution. It can also be an economical substitute for the use of efficient but expensive commercial enzymes.

Removing bitterness

Bitter taste is considered the most important barrier in commercial use of protein hydrolysates in food industry. Low molecular weight peptides account for the bitter taste of hydrolysates. These peptides are known to contain hydrophobic amino acids such as leucine, proline, phenylalanine, and tyrosine (Ishibashi et al., 1988; Meinlschmidt et al., 2016). In this regard, Aubes-Dufau et al. (1995) mentioned that the peptides with molecular weights up to roughly 6 kDa and Q values exceeding 1400 cal·mol^{-1} can be considered bitter; Q value is a predictive index for bitterness of a given peptide and is defined as the hydrophobicity of the side chain of amino acids in the peptide (Ney, 1971). Bitterness of hydrolysates is not only caused by hydrophobic amino acid themselves but by their locations in peptide sequence, as well (Spellman et al., 2009). Hydrophobic amino acids caused more bitterness when they were inside the peptide chain rather than the N- or C-terminus of peptides (Matoba and Hata, 1972).

FitzGerald and O'Cuinn (2006) listed different methods of removing bitterness from protein hydrolysates: (i) absorption of bitter peptides on activated carbon; (ii) chromatographic removal using different matrices; (iii) selective extraction with alcohols; (iv) masking hydrolysates by addition of polyphosphates, specific amino acids such as Asp and Glu, and α-cyclodextrins; (v) mixing hydrolysates with intact protein samples; (vi) formation of plasteins; and (vii) cross-linking using transglutaminase. However, they also pointed to drawbacks of these methods such as loss of some amino acid residues and decrease in solubility.

Recently, the formation of plasteins, which are less soluble aggregated macromolecular structures formed by incubation of higher concentrations of the hydrolyzed proteins or peptides with suitable proteases, has gained an increasing attention (Udenigwe and Rajendran, 2016). Plasteins were found to have lower bitterness than the peptides in hydrolysates (Liu et al., 2014). Proposed mechanisms of plastein formation include peptide condensation, transpeptidation, and physical forces in peptide aggregation (for more elaboration on the mechanisms, readers are referred to Gong et al., 2015). Plastein reaction was successfully adopted to reduce bitterness in the hydrolysates prepared from bovine red blood cells (Synowiecki et al., 1996) and yellowfin tuna (Zhao et al., 2015) as well as in synthetic dipeptides (Stevenson et al., 1998).

One of the most important factors influencing the taste of hydrolyzed protein is the sequence and nonpolarity of amino acids like F, W, Y, I, P, and H. Bitter taste perception of these amino acids can be changed by addition of α-cyclodextrin to protein hydrolysate resulting in reduction of its bitterness (Linde et al., 2009). In addition, microencapsulation of hydrolysates plus incorporation of masking agents are effective alternatives for attenuation of bitterness in hydrolysates. Daskaya-Dikmen et al. (2017) claimed that encapsulation of peptides in hydrolysates is the most favorable technique in order to reduce bitterness. Favaro-Trindade et al. (2010) reported that bitter taste decreased when casein hydrolysates were spray-dried and mixed with gelatin and soy protein isolate as carriers. It is noteworthy that the debittering ability of gelatin might be attributed to its endogenous amino acid glycine to mask bitterness in hydrolysates (Stanley, 1981). Furthermore, Ma et al. (2013) compared freeze- and spray-drying of whey protein hydrolysates and found that the latter had higher efficiency of microencapsulation and therefore, resulted in less bitter hydrolysates.

The protease used to hydrolyze protein can also affect the taste of final product. Recently, Cheung et al. (2015) found that exopeptidase-treated hydrolysates are less bitter and have higher levels of umami and salty tastes as well as increased overall acceptability compared to those produced by endopeptidases. Moreover, when determing the influence of sequential hydrolysis using endo- and exo-peptidase on bitter taste of protein hydrolysates from wheat gluten, Liu et al. (2016) found that the hydrolysate produced within a 300-min reaction with Proteax had the lowest bitterness. Raksakulthai and Haard (2003) also indicated application of exopeptidases to reduce bitter taste of protein hydrolysate. Moreover, Nishiwaki et al. (2002) reported that an aminopeptidase from the edible basidiomycete *Grifola frondosa* can yield less bitter protein hydrolysates. However, Hou et al. (2011) claimed that all these procedures lead to a serious loss of essential amino acids. They suggested that using a combination of exo- and endopeptidases along with high-pressure cooking can prevent the loss.

Besides, Newman et al. (2015) recommended the use of sweeteners and flavoring agents to reduce bitterness of protein hydrolysates. They added sucralose as a sweetener and vanilla as a flavoring agent to a model beverage containing sodium caseinate hydrolysate and concluded that this method was very effective in reducing the bitter taste of the beverage caused by the hydrolysate.

Although several methods have been proposed to reduce or remove bitterness from protein hydrolysates, the majority of them seemingly suffer from side effects like loss of amino acids and alteration of functional properties of the bioactive peptides obtained by the hydrolysis process. Besides, to the best of our knowledge, no study has been done to assess economic feasibility of the hitherto-proposed debittering solutions in industrial scale. Therefore, future studies should be directed towards finding the most effective and economical debittering methods with the least side effects in order to operationalize the adoption of bioactive peptides from hydrolyzed proteins in foodstuffs.

Fractionation, purification and identification of bioactive peptides including bioinformatics-driven approaches

Fish protein hydrolysates are generally complex mixtures of peptides with different chain lengths and amino acids composition, as well as other nondesired compounds such as enzymes, nondegraded proteins and free amino acids. Hence, fractionation technologies are required to separate peptides from residual enzymes, and remaining nonreacted native proteins and free amino acids, which can induce allergenic responses and lead to osmotically-unbalanced products, respectively. Besides, the fractionation process makes it possible to control the molecular-weight distribution of the hydrolysates and to concentrate the desired bioactive or functional peptides (Akin et al., 2012). For that purpose, pressure-driven membrane techniques (e.g., ultrafiltration) are commonly used since they can easily be scaled-up (Langevin et al., 2012). Although most of the studies reported in the literature utilize polymeric membranes (Chabeaud et al., 2009; Jiang et al., 2010; Hwang et al., 2016), ceramic membranes are preferred at industrial scale due to their high chemical resistance, wider operational limits of pH and temperature, as well as extended operational lifetime (Lin et al., 2011; Espejo-Carpio et al., 2014b). In addition, tangential-flow filtration is recommended instead of cross-flow filtration membranes in order to limit membrane fouling (Prieto et al., 2010b).

Over the past few decades, due to the increasing interest in the production of natural biomolecules, there has been a boom in the number of publications dealing with the concentration of bioactive peptides by ultrafiltration. Generally, fractions containing low-molecular weight peptides have been reported to exhibit higher bioactivities in vitro. For instance, numerous studies indicate that peptide fractions <1 kDa showed the strongest Angiotensin-I converting enzyme (ACE)-inhibitory activity, independently of the type of raw protein (e.g., terrestrial plants or fish) (Zhao et al., 2007; Zou et al., 2014; Wu et al., 2016a, b). Nevertheless, these differences on ACE-inhibitory activity depending on the molecular weight of the peptides might not be observed in vivo as reported for salmon protein hydrolysate fractions (Ewart et al., 2009). As another example, low molecular weight peptides (<1 kDa), obtained from the hydrolysis of whey protein isolate, have also been reported to exhibit a significant increase in the Fe^{2+} chelating activity when compared to larger peptide fractions (O'Loughlin et al., 2014). On the other hand, higher molecular weight peptides (1–3 kDa), obtained from hydrolysis of fish protein, were found to show the highest radical scavenging activity when compared to other peptide fractions (<1, 3–5 and 5–10 kDa) (Kim et al., 2007).

Recently, more complex fractionation processes have been studied for the concentration of bioactive peptides. As an example, target bioactive peptides with similar molecular weight, which cannot be separated by pressure-driven membranes, have been concentrated by electrodialysis with ultrafiltration membranes (Doyen et al., 2014; He et al., 2016). Furthermore, sequential ultrafiltration and nanofiltration stages have also been tested in order to obtain even more concentrated peptide fractions with a reduced salt content (Langevin et al., 2012; Ranamukhaarachchi et al., 2013). In contrast, fractionation techniques are seldom applied to improve functional properties of protein hydrolysates. Among the few studies found in the literature, Jeon et al. (1999) reported that fractions from cod frames hydrolysates containing large peptides (>30 and >10 kDa) showed excellent emulsifying properties and whippability. Likewise, Taheri et al. (2014) indicated that polypeptides (>50 kDa) obtained from proteins contained in herring brine presented higher emulsion activity index, when compared to fractions having peptides with lower molecular weight. This indicates that only a limited hydrolysis of native proteins is required to improve these technological properties (e.g., emulsifying and foaming).

Further purification and identification of bioactive peptides are required in order to determine their structure-activity relationship. Initial peptide separation is normally performed by using fast protein liquid chromatography (FPLC), employing gel permeation or ion-exchange columns (Sampath Kumar et al., 2011; Vavrusova et al., 2015). The fraction containing the most active peptides is then subjected to high pressure liquid chromatography (HPLC) separation using a reverse-phase column (RP-HPLC). This allows obtaining peptides subfractions with different hydrophobic behavior, but more than one RP-HPLC round will be required in order to obtain highly pure peptides in a sufficient amount (de Gobba et al., 2014a; Chi et al., 2015; Ruiz-Giménez et al., 2012). Furthermore, hydrophilic interaction liquid chromatography (HILIC) has recently been suggested for an improved separation of homologous short peptides (Le Maux et al., 2015). Finally, these chromatographic techniques are coupled to mass spectrometry (MS), in particular to tandem MS (MS/MS), for peptide sequence determination. Traditional identification approaches, which require the knowledge of the parent protein sequences, match tandem spectra with theoretical spectra derived from predicted peptides in a protein library (Espejo-Carpio et al., 2013; Gu and Wu, 2013; de Gobba et al., 2014b). Primary structure of proteins can be accessed from online databases such as UniProtKB/Swiss-Prot or NCBI and the identification process can be carried out by using database search engines (e.g., Mascot) (Dallas et al., 2015; Le-Maux et al., 2015). On the other hand, *de novo* sequencing approach does not require a protein library and deduces peptide amino acid sequence by calculating mass differences between fragments from the tandem mass spectra (Girgih et al., 2014; García-Moreno et al., 2015). For that purpose, generally employed programs are Peaks (Marques et al., 2015) and PepSeq (Liu et al., 2015). Alternatively to MS techniques, automated Edman degradation has been also widely employed for sequencing amino acids in a highly purified peptide (Je et al., 2005a; Sheih et al., 2009a, b; Chi et al., 2015).

Other advances in bioinformatics, also known as *in silico* analysis or software-based methods, allow predicting and identifying cryptic peptides likely to exhibit bioactivities, elucidate structure-function relationships and propose mechanisms of action (Li-Chan, 2015). BIOPEP, a database mainly focused on peptides from food, is generally employed to determine the occurrence frequency of embedded bioactive peptides in the primary structure of the food proteins of interest (Udenigwe, 2014; Lacroix and Li-Chan, 2012). Peptide cutter programs (e.g., ExPASy) are used to generate peptide profiles *in silico*

from specific primary protein structures using enzymes of known specificity (Udenigwe et al., 2013; Nongonierma and FitzGerald, 2016a). Peptide cutters have been also employed to assay the potential cleavage by gastrointestinal tract enzymes of bioactive peptides obtained experimentally (Fitzgerald et al., 2012). Quantitative structure activity relationship models (QSAR) have been successfully used to predict biological activity of peptide sequences based on physicochemical descriptors (e.g., size, charge, polarity, sequence, etc.) (Sánchez-Rivera et al., 2014). For instance, QSAR approaches have been applied to study ACE-inhibitory, antioxidant and antimicrobial peptides (see Jahangiri et al., 2014; Nongonierma and Fitzgerald, 2016b). Finally, molecular docking simulations have also been developed to predict possible interactions of peptides with proteins (e.g., active sites of enzymes), which are the target of the biological activity (Li-Chan, 2015). Examples in the literature include studies on ACE as well as DPP-IV inhibitory peptides (Lin et al., 2017; Nongonierma et al. 2014). Thus, *in silico* tools may expedite the discovery and production of bioactive peptides from food proteins, although they still have some limitations (e.g., do not consider secondary, tertiary and quaternary structures of proteins to predict cleavage sites; and assume enzymes with stringent substrate specificity, which is not always the case in food applications where complex protease-proteins interactions occur) (Li-Chan, 2015; Nongonierma and FitzGerald, 2016a; Udenigwe, 2014).

Bioactivity of peptides

Effects on immune system

An overview of reported effects on immune system is given in Table 1, which also shows the suggested peptides responsible for the effects.

Antifungal effect

Past few decades have witnessed a dramatic increase in fungal infections, especially the invasive ones with a high potential of claiming lives (Wang et al., 2016). Not only are they perilous for humans, they might have notorious influence on plants and may even kill them (Luna-Vital et al., 2015). Therapeutic options to fight against pathogen fungi seem to be very restricted since there are only few antifungals specialized for the pathogens (Wang et al., 2016). In addition, a global concern on the use of synthetic antifungals has directed academic efforts toward finding natural alternatives to combat against trouble-making fungi.

In nature, antifungal peptides are considered the first defense barrier between the organism and its surroundings. These peptides are small cationic and amphipathic molecules with not more than 50 amino acids (Shekh and Roy, 2012). Antifungal proteins and peptides have been isolated from different sources (Table 1).

Antimicrobial effect

Drug resistance in bacteria has turned out to be a major problem in using antibiotics in recent years. Add to this the current concern on using chemical preservatives in foods in order to avoid different kinds of spoilage including microbial decay. In this regard, one of the most interesting research breakthroughs is the discovery of the so-called antimicrobial peptides (AMPs) with a potential effect on even drug-resistant species (Tang et al., 2015). Production of AMPs can guarantee the innate immunity resistance against different pathogens. AMPs are majorly small cationic molecules and they are very favorable since their synthesis can be done with low metabolic cost and they have the capability to diffuse rapidly to the point of infection (Pisuttharachai et al., 2009). AMPs have a very wide scope in terms of their physiological roles, many of which are still to be determined. These roles range from killing microbes to modulating the immune system through increase in phagocytosis (Battison et al., 2008). It seems very important to find new resources from which the very promising alternatives for current antibiotics, i.e., AMPs, can be obtained.

Antimicrobial proteins and peptides have been obtained from a variety of sources such as aquatic organisms like shrimp (Cuthbertson et al., 2002), sole (Oren and Shai, 1996), flounder (Cole et al., 1997), and anchovy (Tang et al., 2015), plants (Capriotti et al., 2015), blood (Fogaca et al., 1999), milk (McCann et al., 2006), and egg (Mine et al., 2004), to name a few. One of the latest investigations to derive antimicrobial peptides from natural sources was the work performed by Capriotti et al. (2015). They identified antimicrobial peptides from soybean seeds and milk protein generated by simulated gastrointestinal digestion (Capriotti et al., 2015).

Antiviral effect

Bioactive peptides and hydrolysates were found to have antiviral activities against different species of viruses such as HSV-1 and HSV-2 (Conlon et al., 2014a). These peptides and hydrolysates were produced from different sources, e.g., oyster (Lee and Maruyama, 1998; Shimizu et al., 2009), crab (Miyata et al., 1989; Murakami et al., 1991; Masuda et al., 1992), mussel (Mitta et al., 2000), and even, different frog species skins (Conlon et al., 2014b). Antiviral effect of these peptides has been claimed to be in two ways: one through direct inactivation of virus particles and the other via interference in reproductive cycle of virus (Conlon et al., 2014a, b). Antiviral peptides from natural sources are especially appealing because they require a rather short contact time to induce their effect (Conlon et al., 2014a, b).

Immunomodulatory effect

Proteins and peptides obtained from plant and animal sources (Table 1) have been found to improve lymphocyte proliferation, natural killer (NK), cell activity, antibody synthesis and cytokine regulation (Singh et al., 2014). Recently, milk bioactive peptides released by selected *Lactobacillus helveticus* strains (Elfahri et al., 2014) and the frog skin host-defense peptides (Mechkarska et al., 2014) were shown to induce stimulatory influence on the production of cytokines with pro- and anti-inflammatory effects. In addition, an immunomodulatory peptide derived from zebrafish phosvitin has been suggested to up-regulate the expression of the anti-inflammatory and down-regulate the expression of the pro-inflammatory cytokine genes (Ding et al., 2012).

Parker et al. (1984) detected a hexapeptide with amino acid sequence of VEPIPY with immunostimulatory effect. The

Table 1. Effects of bioactive peptides on immune system.

Effects		Origin	Amino acid sequence (in single-letter code)	Reference
Antifungal peptides	AS	Crab	RRWCFRVCYRGFCYRKCR, RRWCFRVCYKGFCYRKCR, RWCFRVCYRGICYRKCR, KWCFRVCYRGICYRRCR, YLAFRCGRYSPCLDDGPNVNLYSCCSFY, DYDWSLRGPPKCATYGQKCRTW SPPNCCWNLRCKAFRCRPR	Miyata et al., 1989; Murakami et al., 1991; Ohta et al., 1992; Kawabata et al., 1996; Osaki et al., 1999
		Blood of immune-challenged and untreated mussels (*Mytilus edulis*)	DCCRKPFRKHCWDCTAGTPYYGYSTRNIFGCTC	Charlet et al., 1996
		Bass	FFHHIFRGIVHVGKTIHKLVTG	Lauth et al., 2002
		Salmon	—	Kamal and Motohiro, 1986
		Sea hare	—	Woyke et al., 2001; Pettit et al., 1998
		Shrimp	YRGGYTGPIPRPPPIGRPPFRPVCNACYRLSVSD ARNCCIKFGSCCHLVKG, QVYKGGYTRPIPRPPPFV RPLPGGPIGPYNGCPVSCRGISFSQARSCCSRLGRCCHVGKGYSG, LVVAVTDGDADSAVPNLHENTEYNHYGSHGVY, VTDGDADSAVPNLHENTEYNH YGSHGVYPDK, FEDLPNFGH IQVKVFNHGEHIHH, PEVYKGGYTRPIPRPPPFVRPLPGGPIGPYNG CPVSCRGISFSQARSCCSRLGRCCHVGKGYS, VYKGGYTRPVPRPPPF VRPLPGGPIGPYNGCP VSCRGISFSQARSCCSRLGRCCHVGKGYS, VYKGGYTRPIPRPPFVRPVPG GPIGPYNGCPVS CRGISFSQARSCCSRLGRCCHVGKGYS	Destoumieux et al., 1991, 2000; Destoumieux-Garzon et al., 2001
		Oyster(Muscle)	CLEDFYIG	Liu et al., 2008
	TP	Mushroom	AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN, ATRVVYCNRRSGSV VGGDDTVYYEG, AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN	Wang and Ng, 2004; Lam and Ng, 2001
		Traditional Chinese medicinal herbs	—	Zhang et al., 2013
		Bean	KTCENLADTFRGPCFATSNC,KTCENLADTYKGPCFTTGSCDDHCK, KTCENLADTYKGPCFTTG, TENLADTYWGPPFTRGS, KTCENLADTY, KTCGNLANQYYPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCTK, KTYENLADTYKGPYFTTGSHDDHYKNKEHLRSGRMRDDFF, KTYENLADTYKGPYFTTGSHDDHYKNKEHLRSGRYRDDFF	Wong et al., 2012; Chan et al., 2012; Chan and Ng, 2013; Lam and Ng, 2013; Leung et al., 2008; Lin et al., 2010; Wang and Ng, 2007; Wu et al., 2011
	TA	Venom of the social wasp (*Polybia paulista*)	ILGTILGLLKSL	Wang et al., 2016
Antimicrobial peptides	AS	Oyster(Muscle)	CLEDFYIG	Liu et al., 2008
		Bass	FFHHIFRGIVHVGKTIHKLVTG	Lauth et al., 2002
		Crab	RRWCFRVCYRGFCYRKCR,RRWCFRVCYKGFCYRKCR,RWCFRVCYRGI CYRKCR, KWCFRVCYRGICYRRCR, YLAFRCGRYSPCLDDGPNVNLYSCCSFY, DYDWSLRGPPKCATYGQKCRTWSPPNCCWNLRCKAFRCRPR	Miyata et al., 1989; Murakami et al., 1991; Osaki et al., 1999; Kawabata et al., 1996
		Crayfish	FKVQNQHGQVVKIFHH	Lee et al., 2002
		Flounder	GWGSFFKKAAHVGKHVGKAALTHYL	Cole et al., 1997
		Loach	RQRVEELSKFSKKGAAARRRK	Park et al., 1997
		Lobster	IVENTSLEPHAGRCLLHTMCVKGDFTPPSPIR, QYGNLLSLLNGYR MMKLVLLCVLGLAV,MLKLVLLCVLGLALG, MLKLVLLCVLGLALG, MLRLVLLCVLGLAVG	Pisuttharachai et al., 2009; Battison et al., 2008
		Salmon	—	Uyttendaele and Debevere, 1994
		Atlantic salmon rest raw material	—	Opheim et al., 2015
		Shrimp	MRLVVCLVFLASFALVCQG, YRGGYTGPIPRPPPIGRPPFRPVCNA CYRLSVSDARNCCIKFGSCCHLVKG, QVYKGGYTRPIPRPPPFVRPLPGGPIGPYNGCPV SCRGISFSQARSCCSRLGRCCHVGKGYSG, PEVYKGGYTRPIPRPPPFVRPLPGGPIGPYNGCP VSCRGISFSQARSCCSRLGRCCHVGKGYS, VYKGGYTRPVPRPPPF VRPLPGGPIGPYNGCP VSCRGISFSQARSCCSRLGRCCHVGKGYS,VYK GGYTRPIPRPPFVRPVPGGPIGPYNGCPVSCR GISFSQARSCCSRLGRCCHVGKGYS	Cuthbertson et al., 2002; Destoumieux et al., 1991, 2000
		Sole	GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	Oren and Shai, 1996

(*Continued on next page*)

Table 1. (*Continued*)

Effects		Origin	Amino acid sequence (in single-letter code)	Reference
		Marine mussels	HPHVCTSYYCSKFCGTAGCTRYGCRNLHRGKLCFCLHCSR, HSHACTSYWCGKFCGTASCTHYLCRVLHPGKMCACVHCSR, QSVACRSYYCSKFCGSAGCSLYGCYLLHPGKICYCLHCSR, SCASRCKGHCRARRCGYYVSVLYRGRCYCKCLRC, GFGCPNNYACHQHCKSIRGYCGGYCASWFRLRCTCYRCG, GFGCPNDYPCHRHCKSIPGRYGGYCGGXHRLRCTC, GFGCPNDYCHRHCKSIPGRXGGYCGGXHRLRCTCYR, GCASRCKAKCAGRRCKGWASASFRGRCYCKCFRC	Padhi and Verghese, 2008; Balseiro et al., 2011; Mitta et al., 2000; Charlet et al., 1996
		Anchovy cooking wastewater	GLSRLFTALK	Tang et al., 2015
		Penaeid shrimp	FEDLPNFGHIQVKVFNHGEHIHH	Petit et al., 2016
		Zebrafish phosvitin	—	Ding et al., 2012
		Tegillarca granosa hemoglobin	PSVQDAAAQISADVKK, VLASLNFGDR,ISAAEFGK, ISAEAFGAINEPMK, GHAITLTYALNNFVDSLDDPSR, MGSYYSDECAAAWAALVAVVQAAL, LNGHGLTLWYGIQNFVDQLDNADDLEDVARK	Bao et al., 2016
	TP	Traditional Chinese medicinal herbs	—	Zhang et al., 2013
		Soybean	FVLPVIRGNGGGIQVA, IIVVQGKGAIGF, WAISKDISEGPPAIKL, ITLAIPVNKPG, LAFPGSAKDIENLIKSQ, ASRGIRVNGVAPGPVWTPIQPA, IVTVKGGLRVTAPA, KIGGIGTVPVGRVETGVLKPGMVV, LFVLSGRAIL, GIRVNGVAPGPVWTPIQPA, LAGSKDNVIRQIQKQVKEL NVLKVIPAGSSSGAKKA, IIIAQGKGALGV, SGGIKLPTDIISKISPLPVLKEI, SGGIKLPTDIISKISPLPV, MIIIAQGKGALGV, IIVVQGKGAIG, VLDFNSVADLTKGNVGGLIGTGL, ASLGGLQNVSGINFLIK, AIVILVINEGDANIELVGIK, VDINEGALLLPHFNSKAIV, VLSGRAILTLV, GKVKIGINGFGRIGRLV, IIYALNGRALVQV,IYALNGRALIQV	Capriotti et al., 2015
	TA	Bovine blood	FLSFPTTKTYFPHFDLSHGSAQVKGHGAK, VLSAADKGNVKAAWGKVGGHAAE, VTLASHLPSDFTPAVHASLDKFLANVSTVL QADFQKVVAGVANALA HRYH, STVLTSKYR,TSKYR,VTLASHLPSDFTPAVHASLDKFLAN VSTVLTSKYR, VNFKLLSHSLLVTLASHL	Fogaca et al., 1999; Froidevaux et al., 2001; Daoud et al., 2005; Nedjar-Arroume et al., 2006; Jang et al., 2008
		Beef muscle	GFHI, DFHING, FHG, GLSDGEWQ	Jang et al., 2008
		Bovine hemoglobin	VNFKLLSHSLLVTLASHL, TKAVEHLDDLPGALSELSDLHAHKLRVDPVNFKLLSHSLL, LDDLPGALSELSDLHAHKLRVDPVNFKLLSHSL,KLLSHSL,LLSHSL	Hu et al., 2011; Adje et al., 2011
		Deer, sheep, pig, and cattle blood	—	Bah et al., 2016
		Frogs	IKIPAVVKDTLKKVAKGVLSAVAGALTQ, IKLSPETKDNLKKVLKGAIKGAIAVAKMV, LKIPGFVKDTLKKVAKGIFSAVAGAMTPS, IKIPAFVKDTLKKVAKGVISAVAGALTQ, IKIPPIVKDTLKKVAKGVLSTIAGALST, IKLSPETKDNLKKVLKGAIKGAIAVAKMV, GLVGTLLGHIGKAILG, GLVGTLLGHIGKAILS	Mechkarska et al., 2012; Mechkarska et al., 2013; Mechkarska et al., 2014; Conlon et al., 2014
		Bovine mammary epithelial cell line	—	Malvisi et al., 2015)
		Venom of the social wasp *Polybia paulista*	ILGTILGLLKSL,IDWKKLLDAAKQIL	Souza et al., 2005
	DE	Milk	LRLKKYKVPQL, VYQHQKAMKPWIQPKTKVIPYVRYL, IKHQGLPQE, VLNENLLR, SDIPNPIGSENSEK	Mohanty et al., 2015; McCann et al., 2006; Hayes et al., 2006
		Human milk	EQLTK, GYGGVSLPEWVCTTFALCSEK, CKDDQNPHISCDKF, GRRRRSVQWCAVSQPEATKCFQWQR NMRKVRGPPVSCIKRDSPIQCIQA	Pellegrini et al., 1999; Hunter et al., 2005
		Egg	IVSDGDGMNAW, HGLDNYR	Mine et al., 2004; Mine and Kovacs-Nolan, 2006
		Bovine milk	YQEPVLGPVRGPFPI,YQEPVLGPVRGPFPIIV,EVFGKEKVN, SDIPNPIGSENSEK,RPKHPIKHQGLPQEVLNENLLRF,VLNENLLR	Dallas et al., 2016
Antiviral peptides	AS	Oyster(Muscle)	LLEYSI,LLEYSL	Lee et al., 1998
		Crab	KWCFRVCYRGICYRRCR, RRWCYRKCYKGYCYRKCR	Murakami et al., 1991; Masuda et al., 1992
		Sponge	—	Plaza et al., 2007; Plaza et al., 2009; Andjelic et al., 2008
	TP	Mushroom	AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN	Lam and Ng, 2001
		Bean	KTCGNLANQYYPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCTK	Lin et al., 2010
	TA	Frog skin	ALWMTLLKKVLKAAAKAALNAVLVGANA	Bergaoui et al., 2013
Immunomodulatory peptides	AS	Atlantic salmon (*Salmo salar*)	—	Opheim et al., 2015
		Musca domestica larvae	—	Sun et al., 2014
		Chlorella vulgarian	—	Morris et al., 2009
		Zebrafish phosvitin	—	Ding et al., 2012

(*Continued on next page*)

Table 1. (*Continued*)

Effects		Origin	Amino acid sequence (in single-letter code)	Reference
	TP	Soybean	MITLAIPVNKPGR, MITLAIPVN, MITL, HCQRPR, QRPR, MITLAIPVNKPGR	Yoshikawa et al., 2000; Singh et al., 2014; Capriotti et al., 2015
		Rice	GYPMYPLPR	Takahashi et al., 1994
		Mushroom	—	Sheu et al., 2004; Lin et al., 2013
		Wheat	—	Horiguchi et al., 2005
		Buckwheat pollen	RKYVD	Liu et al., 1998
		Turmeric (*Curcuma longa*)	—	Aravind and Krishnan, 2016
		Chickpea	—	Clemente et al., 1999
	TA	Frog skin	GLVGTLLGHIGKAILG, GLVGTLLGHIGKAILS, IKLSPE TKDNLKKVLKGAIKGAIAVAKMV	Mechkarska et al., 2014; Conlon et al., 2014; Mechkarska et al., 2013
		Bovine mammary epithelial cell line	—	Malvisi et al., 2015
	DE	Egg	—	Xie et al., 2002; Fan et al., 2003
		Milk	TTMPLW, YPFPAVPYPQRTTMPLW, YQEPVLGPVR, LLY	Meisel, 2005; Mohanty et al., 2015; Elfahri et al., 2014; Hernandez-Ledesma et al., 2004; Berthou et al., 1987
		Camel milk	QEPVPDPVRGLHP	El Hatmi et al., 2016
		Whey	—	Mercier et al., 2004
		Bovine milk	PGPIPN, YQEPVLGPVRGPFPIIV, PGPIPN, LYQEPVLGPVRGPFPIIV	Boutrou et al., 2013; Dallas et al., 2016
		Bursa of Fabricius (BF) in chicken	YEYAY, RMYEE, GPPAT, AGCCNG, RRL	Feng et al., 2012
		Human milk	VEPIPY	Parker et al., 1984
		Egg	SVNVHSSL,YRGGLEPIN	Goldberg et al., 2003
Cytomodulatory peptides	DE	Bovine milk	KAVPYPQ,PYPQ, RTLGYLE,RTLGYL, YPFPGPI YVPFPYPFPG, AVP YPQR,RETIESLSSSEESIPEYK, QPTIPFFDPQIPK	Kampa et al., 1997; Nagaune et al., 1989; Hernandez-Ledesma et al., 2004
		Camel milk	KRKEMPLLQSPV	El Hatmi et al., 2016
		Casein	EPVLGPVRGP	Zhao et al., 2014
Antiproliferative, anti-tumor, and anti-cancer peptides	TP	Bean (*Phaseolus vulgaris* L.)	KTYENLADTYKGPYF TTGSHDDHYKNKEHLRSGRMRDDFF, KTCGNLANQYYTPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCT K, KTYENLADTYKGPYFTTGSHDDHYKNKEHLRSGRYRDDFF	Wang and Ng, 2007; Lin et al., 2010; Wu et al., 2011
		Mushroom Flammulina velutipes	—	Lin et al., 2013
		Soybean	XMLPSYSPY, SKWQHQQDSCRKQKQGV NLTPCEKHIMEKIQGRGDDDDDDDDD	Kim et al., 2000; Valjakka et al., 1997
		Turmeric (*Curcuma longa*)	—	Aravind and Krishnan, 2016
		Bean	KTCGNLANQYYPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCTK	Lin et al., 2010
	TA	Frog skin	IKLSPETKDNLKKVLKGAIKGAIVAKMV, GLWSKIKEAAKAAGKAALNAVTGLVNQGDQPS, GLVG TLLGHIGKAILG,GLVGTLLGHIGKAILS	Attoub et al., 2013; Conlon et al., 2007; Mechkarska et al., 2014; Conlon et al., 2014
	AS	Sea hare (*Dolabella auricularia*)	XVXXX	Madden et al., 2000; Pettit et al., 1998; Turner et al., 1998; Vaishampayan et al., 2000
		Musca domestica larvae	—	Sun et al., 2014
		Fish sauce	—	Lee et al., 2003, 2004
		Sea hare (*Dolabella auricularia*)	XVXXX	Madden et al., 2000
		Cod, plaice, salmon	—	Xhindoli et al., 2016; Ngo et al., 2012
		Tuna muscle	LPHVLTPEAGAT, PTAEGGVYMVT	Hsu et al., 2011
		Fish backbone	—	Zhang et al., 2013; Ngo et al., 2012
		Sardine muscle	VY	Matsui et al., 2005
		Shrimp shell	—	Kannan et al., 2011
		Sea slug (*Pleurobranchus forskalii*)	—	Wesson and Hamann, 1996
	DE	Bovine Milk	VENLHLPLPLL,NLHLPLPLL, ENLHLPLPLL, ALNENLLRFFVAPFP EVFG, LNENLLRFFVAPFPEVFG, NENLLRFFVAPFPEVFG, ENLLRFFVAPFPEVFG, FVAPFPEVFG	Juillerat-Jeanneret et al., 2011
Antimutagenic and antigenotoxic	DE	Kefir	—	Guzel-Seydim et al., 2011
	TA	Bovine plasma, globulin and albumin	—	Park and Hyun, 2002
		Silk fibroin	—	Park et al., 2002

AS, TP, TA, and DE stand for aquatic sources, terrestrial plants, terrestrial animals, and dairy & eggs, respectively.
Uncommon amino acids are denoted by "X."

peptide was claimed to stimulate in vitro phagocytosis of sheep red blood cells by murine macrophages and to have in vivo protective effect in mice against lethal infection caused by *Klebsiella pneumonia* (Parker et al., 1984).

On the other hand, application of bioactive peptides from different resources has been limited due to their potential antigenicity and immunoreactivity in the body. In this regard, protein hydrolysates with hypoimmunoreactive effect are more favorable to be used in industrial products. Clemente et al. (1999) obtained extremely hypoimmunoreactive protein hydrolysates from chickpea by sequential treatment using endo- and exopeptidases. They defined hypoimmunoreactivity by the loss of antigenicity through reduction in the interaction capacity of antigenic determinants with specific antibodies (Clemente et al., 1999).

Cytomodulatory effect

Bioactive peptides obtained from different sources (Table 1) have been shown to have cytomodulatory effect. Zhao et al. (2014) identified peptides from casein with cytomodulatory effect (Zhao et al., 2014). Cytomodulation can be of a great health importance since it is related to cell proliferation and apoptosis as two attributes of cell viability (Zhao et al., 2014). These peptides can also regulate immune cells and therefore, they can play an important role in regulation of immune system (Elfahri et al., 2014). However, the term cytomodulation seems to include a wide spectrum of applications with key roles in controlling cancer, tumor, and other cell-related disorders. In other words, there is seemingly some conceptual overlap between immunomodulation, cytomodulation, anticancer, antitumor, etc. Nonetheless, we present a separate part as follows to give a better overview of peptide bioactivity.

Antiproliferative/antitumor/anticancer effects

Cancer is one of the most important diseases in the world and millions of people die annually as a consequence of this dangerous disorder. It is generally characterized by the presence of transformed cells in different tissues. In other words, the carcinogenic cells start out-of-control multiplication in the site they belong to without rendering the role they are originally supposed to. The transformed invasive cells can even cross through their own sites and enter, say, blood vein to cause more severe problems (Luna-Vital et al., 2015). There are several chemotherapeutics and targeted antineoplastic agents commercially available; however, although they prove to be very efficient against tumor and cancer, there have also been serious complaints regarding their adverse side-effects. In addition, resistance to chemotherapy-based treatments has also increased concerns regarding cancer cure since some patients experience tumor relapse with the new tumor being resistant to already-adopted treatments (Sun et al., 2014). Taken together, academic interest has shifted toward finding dietary agents in order to block or at least alleviate the effects of tumor or even to prevent outbreak of cancer. Bioactive peptides from different sources have been found to have antitumor effects (Attoub et al., 2013; Lin et al., 2013; Sun et al., 2014; Luna-Vital et al., 2015) (Table 1). Yet, no single mechanism has been detected for the peptides to cause tumor cell death, but their action mechanism includes nonspecific perturbation of the cell membrane and subsequent insertion into the lipid bilayer so as to disrupt cell membrane (Attoub et al., 2013).

Bioactive peptides from natural resources have also been found to fight against proliferation of trouble-making cells. Several studies have shown that peptides from different sources such as sea hare (Pettit et al., 1998; Turner et al., 1998; Madden et al., 2000; Vaishampayan et al., 2000; Woyke et al., 2001), fish sauce (Thang and Zhao, 2015; Bah et al., 2016), and cod (Xhindoli et al., 2016) were able to block proliferation of carcinogenic cells. However, it seems there is still a long way in order to make commercial use of these potentially potent anticancer peptides to treat different kinds of cancer. For example, clinical intervention trials are needed to fully document the effects.

Antigenotoxic and antimutagenic effects

There might be confusion in defining genotoxicity and mutagenicity. In general, genotoxicity is defined as the potential of a chemical agent to impair genetic information within a cell; such impairment might cause mutation (mutagenicity) and cancer. In other words, genotoxics include a broader spectrum of harmful agents than mutagens; simply put, although all mutagens can be considered genotoxic agents, not all genotoxics are mutagens. Therefore, it is important to find substances in order to shield DNA from possible damage. Park et al. (2002) compared antigenotoxic properties of acidic and enzymatic hydrolysates produced from silk fibroin. They analyzed antigenotoxicity of the isolates in mouse embryo 3T3 cells via Comet assay and concluded that acidic-derived isolates showed higher antigenotoxic activity than those synthetized by the commercial enzyme. Furthermore, they claimed that the treatment containing 10 mg/ml acidic isolates would provide 87 percent protection from DNA damage. They proposed two possible circumstances for antigenotoxicity of the isolates: first, protective interactions between cells and peptide molecules and second, the direct role of peptides to inactivate the mutagen (Park et al., 2002).

Effects on cardiovascular system

Table 2 provides an overview of reported effects of peptides on the cardiovascular system.

Antithrombotic activities

Blood coagulation is a natural and important process required to survive. The process is carried out in abnormal vascular conditions or absence of endothelial surface in the case of vascular injury (Jung and Kim, 2009). However, blood coagulation and clot formation are considered undesirable circumstances in some medical conditions and therefore, antithrombotic agents, especially natural ones, are favored. In this regard, bioactive peptides have been found to have antithrombotic effect (Jolles et al., 1986; Raha et al., 1988; Mazoyer et al., 1990; Chabance et al., 1995; Morimatsu et al., 1996; Shimizu et al., 2009). There are two types of antithrombotic agents: anticoagulants and antiplatelets. The former prevent the formation and growth of clots while the latter inhibit platelet clumping (Li-Chan et al., 2016).

Exogenous anticoagulants from natural sources can be adopted to prolong or stop blood clotting (Jo et al., 2008). This

Table 2. Effects of bioactive peptides on cardiovascular system.

Effects	Origin		Amino acid sequence (in single-letter code)	Reference
Antithrombotic	TP	Bean	LLSL, LSLL, NEGEAH,DNPIFSDHQ, NVLISSMEMKEGA	Oseguera-Toledo et al., 2011
	TA	Porcine muscle	—	Shimizu et al., 2009
	DE	Milk	MAIPPKKNQDK, MAIPPKKNQDK, IAIPPKKIQDK	Jolles et al., 1986; Chabance et al., 1995
		Bovine milk	VPQLEIVPNSA, VPNSA	Boutrou et al., 2013
		Human milk	KRDS, RGDS	Mazoyer et al., 1990; Raha et al., 1988
		Kefir microorganisms on bovine milk	YQEPVLGPVRGPFPIIV, MAIPPKKNQDK	Dallas et al., 2016
		Human lactotransferrin	KRDS	Mazoyer et al., 1990
		Egg	IRW, IQW	Huang et al., 2010; Majumder et al., 2013; Majumder et al., 2015; Majumder et al., 2013
	AS	Blue mussel	EADIDGDGQVNYEE FVAMMTSK	Jung and Kim, 2009
		Echiuroid worm	GELTPESGPDLFVHFLD GNPSYSLYADAVPR	Jo et al., 2008
		Starfish	—	Koyama et al., 1998
		Yellowfin sole	TDGSEDYGILEIDSR	Rajapakse et al., 2005
		Granulated ark	HTHLQRAPHPNALGYHGK	Jung et al., 2007
		Spirulina	LDAVNR, MMLDF	Vo and Kim, 2013
		Salmon	—	Ahn et al., 2012
Anti-diabetic	AS	Dogfish	GIVDHCCRNTCSLYDLEGYCNQ,LPSQHL CGSHLVETLYFVCGQKGFYYVPKV	Anderson et al., 2002
		Shark	GIVDHCCHNTCSLYDLEGYCNQ,LPSQHLCGSHLVETLY FVCGQKGFYYVPKI	Anderson et al., 2002
	TA	Frog skin	GFGSFLGKALKAALKIGANALGGAPQQ,GFLGPLLKLGLKGVAKVIPHLIPSRQQ	Srinivasan et al., 2013
	DE	Egg yolk	LAPSLPGKPKPD	Zambrowicz et al., 2015
		Albumin	KLPGF	Yu et al., 2012
	TP	Canary seed	—	Estrada-Salas et al., 2014
		Momordica charantia	RVRVWVTERGIVARPPTIG	Lo et al., 2016
		Bean	ALVLL,LLSL,DKGGLL,LLLLEDRRR,LSLL,WVVL,LLY,LVLL, FFAAAFT,FFL,DFFL,DFFLS,YAAHEV	Oseguera-Toledo et al., 2015
		Soy	IAVPGEVA,IAVPTGVA,LPYP	Lammi et al., 2015
Hypocholesterolemic and hypotriglyceridemic	AS	Salmon bone frames	—	Wergedahl et al., 2004
	TP	Soy	LPYPRI, AVPGEVA, IAVPTGVA, LPYP	Lammi et al., 2015; Yoshikawa et al., 2000
	DE	β-lactoglobulin	HIRL	Yoshikawa et al., 2000
	TA	Blood (globin)	VVYP, VYP, VTL	Kagawa et al., 1998
		Porcine muscle	DTSEPGACVMILYFHKR	Morimatsu et al., 1996
Anti-anemic	AS	Hairtail	—	Lin et al., 2015
		Fish scale	—	Huang et al., 2015a, b
	TP	Extracts of sugar-cane yeast	GHKR, HKR	De la Hoz et al., 2014
ACE inhibitory & antihypertensive	AS	Sole (frame)	MIFPGAGGPEL	Jung et al., 2006
		Tuna (frame)	GDLGKTTTVSNWSPPKYKDTP	Lee et al., 2010
		Shrimp	VWYHT,VW	Nii et al., 2008
		Muscle of cuttlefish	VELYP	Balti et al., 2015
		Sardine	VY	Matsui et al., 2003; Vercruysse et al., 2008; Tokunaga et al., 2004
		Fish waste	—	Ohba et al., 2003; Morimura et al., 2002
		Sea Bream (scale)	GY, VY, GF, VIY	Fahmi et al., 2004
		Pollack (skin)	GPL, GPM	Byun and Kim, 2001
		Cod (frame)	—	Jeon et al., 1999

(*Continued on next page*)

Table 2. (*Continued*)

Effects	Origin		Amino acid sequence (in single-letter code)	Reference
		Shrimp	FCVLRP, IFVPAF, KPPETV, sequence not found	Benjakul et al., 2009; Hai-Lun et al., 2006
		Oyster (Muscle)	VVYPWTQRF, FY, AW, VW, GW	Wang et al., 2008a, b; Katano et al., 2003
		Oyster (Fermented sauce)	—	Je et al., 2005
		Blue mussel	EVMAGNLYPG	Je et al., 2005
		Cuttlefish(muscle)	VELYP	Balti et al., 2015
		Krill (Muscle)	KLKFV	Kawamura et al., 1992
		Clam (Muscle)	YN	Tsai et al., 2008
		Sardine muscle	VY, IW, IVY, IHPF, YIHPF, VYIHPF	Matsui et al., 2005; Matsufuji et al., 1995
		Bonito muscle	LKPNM,LKP	Fujita and Yoshikawa, 1999
		Thornback ray skin's gelatin	APGAP, GIPGAP	Lassoued et al., 2015
	TP	Soybean	HHL,PGTAVFK, HHL, YLAGNQ, IPPGVPYWT, ASYDTKF, DTKF, NWGPLV, PNNKPFQ, DQTPRVF, YVVFK, TIIPLPV, YVVFK, YLAGNQ, FFL, IYLL, VMDKPQG, NWGPLV, NWGPLV	Shin et al., 2001; Balti et al., 2015; Capriotti et al., 2015; Chen et al., 2003; Kodera and Nio, 2006; Kodera and Nio, 2006
		Soy flour	IRHFNEGDVLVIPPGVPY, IRHFNEGDVLVIPPGVPYW, IYNFREGDLIAVPTG, VSIIDTNSLENQLDQMPRR, YRAELSEQDIFVIPAG	Coscueta et al., 2016
		Bean (*Phaseolus vulgaris* L.)	AFY, FFL,DFFL, DFFLS, NEGEAH, QQEG,DKGGLL, YAAHEV, LLSL, GNAGY, KLMLG, FFAAAFT, LLY, LVLL	Oseguera-Toledo et al., 2015
		Olive (*Olea europaea*)	LTPTSN, LVVDGEGY, FDAVGVK, AFDAVGVK, VGVPGGV, LLPSY, ALMSPH, LFSGGES, LMSPH, LPAGA	Esteve et al., 2015
		Wheat	IAP, IAP	Motoi and Kodama, 2003; Motoi and Kodama, 2003
		Palm kernel	YLLLK, YGIKVGYAIP, LPWRPATNVF,YGIKVGYAIP,GIFE, LPWRPATNVF	Zarei et al., 2015
		Thai rice bran protein	—	Boonla et al., 2015
		Plum (*Prunus Domestica* L.)	MLPSLPK,HLPLL,NLPLL,HNLPLL,KGVL,HLPLLR,HGVLQ,GLYSPH,LVRVQ, YLSF,DQVPR,LPLLR,VKPVAPF	González-García et al., 2014
		Broccoli	YPK	Lee et al., 2006a, b
		Flaxseed protein	KQL,KIQ,LKQ,RAIG,LRSC,KLMS,MAKLM,QQAKQ,QRWI,RWIQ,LRSCQ, LKQLST,KQLSTGC	Udenigwe and Aluko, 2012
		Sesame	LSA,LQP,LKY,IVY,VIY,LVY,MLPAY	Nakano et al., 2006
	TA	Bovine blood	TKAVEHLDDLPGALSELSDLHAHKLRVDPVNFKLLSHSLL, LDDLPGALSELSDLHAHKLRVDPVNFKLLSHSL,KLLSHSL,LLSHSL	Adje et al., 2011
		Bovine tendon	AKGANGAPGIAGAPGFPGARGPSGPQGPSGPP, PAGNPGADGQPGAKGANGAP	Banerjee and Shanthi, 2012
		Beef muscle	GFHI,DFHING, FHG, GLSDGEWQ, VLAQYK	Jang et al., 2008; Jang and Lee, 2005
		Chicken muscle	LKA, LKP, LAP, IKW, FQKPKR, FKGRYYP	Fujita et al., 2000
		Porcine muscle	KRQKYD,EKERERQ, VKKVLGNP, RMLGQTPTK, LGFPTTKTYFPHF,VVYPWT, GR,KR,GP,AA,RP,ARKRVIQY,VKAGF, MYPGIA,VIPEL, RPR,KAPVA, PTPVP, MNPPK, ITTNP, MNPPK, ITTNP, MNP, PPKMNPPK, ITTNP, MNP, NPP, PPK, ITT, TTN, TNP	Katayama et al., 2008; Katayama et al., 2007; Katayama et al., 2003; Yu et al., 2006; Sentandreu and Toldra, 2007; Muguruma et al., 2009; Escudero et al., 2010; Escudero et al., 2012; Nakashima et al., 2002; Arihara et al., 2001; Nakashima et al., 2002
		Animal Meat muscle	IKW, LKP	Vercruysse et al., 2005
		Bovine Achilles tendon collagen	AKGANGAPGIAGAPGFPGARGPSGPQGPSGPP, PAGNPGADGQPGAKGANGAP	Banerjee and Shanthi, 2012
		Bovine Hemoglobin	TKAVEHLDDLPGALSELSDLHAHKLRVDPVNFKLLSHSLL, LDDLPGALSELSDLHAHKLRVDPVNFKLLSHSL,KLLSHSL,LLSHSL	Adje et al., 2011
		Bovine serum albumin	GPK,FH,ER,MR,FR,VPK,YY,LVL,VTK,LTK,SLR,MEN,SLGK,TMR,SVAR,FVAF, VLLR	Lafarga et al., 2016

	DE	Egg	IRW, IQW, LW, KVREGTTY,KVREGT, YREERYPIL, RADHPFL, IVF	Huang et al., 2010; Majumder et al., 2013; Majumder et al., 2013;, Majumder et al., 2015; Fujita et al., 2000; Lee et al., 2006a, b; Miguel and Aleixandre, 2006
		Milk	FALPQYLK,AMKPWIQPK,GPVRGPFPIIV,AVPYPQR,YPVEPFTE,RDMPIQAF, SQSKVLPVPQ,MPFPKYPVEP,IGSENSEKTTMP,NIPPLTQTPV,DKIHPF, VAPFPEVF,FVAPFPEV, VPPIPP, YLLF, KVLPVP, GTW, GVW, NIPP, KVLPVPQ, DKIHPF, YQEPVL, KTTMPLW, HLP, YKVPQ, VLPVPQ, IHPF, EMPFPK, HLPLPL, RGPFPIIV, GPFPIIV, LHLPLP, LHLPLPL, VVVPPF, LTQTPVVVPPF, VRGPFPIIV, LVYPFPGPIPNSLPQNIPP, VLGPVRGPFP, VLGPVRGPFPIIV, KVLPVPQ, EMPFPK, LHLPLP, SKVLPVPQ	Mohanty et al., 2015; Dallas et al., 2016; Mizushima et al., 2004; Chen et al., 2007; Hernandez-Ledesma et al., 2004; Elfahri et al., 2014; Quiros et al., 2009; Maeno et al., 1996; Boutrou et al., 2013
		Casein	VPP, IPP, MKP, PFFVAPFPEVFGK, AVPYPQR, FFVAP, VPP, IPP, LHLPLP, LVYPFPGPIPNSLPQNIPP	Nakamura et al., 2011; Jauhiainen et al., 2010; Ehlers et al., 2011; Yamada et al., 2015; Yamada et al., 2013; Maruyama et al., 1987; Nakamura et al., 1995; Quiros et al., 2007
		Camel milk	VPDPVRGLHP, KVLPVPQ, LHLPLPL, LPP	El Hatmi et al., 2016
		Human milk	HLPLP, WSVPQPK, YPFPPL	Hernandez-Ledesma et al., 2007; Fujita et al., 1996
		Ripened cheese	QNALIVRYTR,EGPKLVAS,KVGTKCCAKP,REKVLASS,PKIDAMREKVLA, KALPMHIRLAF, PVGLVQPASATLYDY, PRKEKLCTTS, NAGPFTPTVNREQLSTS, YQEPVLGPVRG	Sagardia et al., 2013
		Bovine whey	ALPMHIR, YGL,WLAHK, LAMA, YGL,VGINYWLAHK,WLAHK,LAMA, LDAQSAPLR,VFK,VLDTDYK,CMENSA,ALPMH	Mullally et al., 1997; Pihlanto-Leppala et al., 2000
		Human casein	TAP,KTAP,QKTAP,YVP,VRP,VVRP,AVVRP,PAVVRP,NPAVVRP,ANPAVVRP, YANPAVVRP,SHP,PNSHP,AIP,IAIP,IPP,AIPP,IAIPP,PAP,PTPAP,EKTAP, MYY,VAV	Kohmura et al., 1990
		Valyl-Tyrosine	VY	Kawasaki et al., 2000
		Milk products Dahi	SKVYP	Ashar and Chand, 2004
		β-lactoglobulin	ALK,IIAEK,IIAEKTK,IDALNENK,GLDIQK,IDALNENK,TPEVDNEALEK, IIVTQTMK,ALPMHIR,IPAVFK,VAGTWY,VLVLDTDYK,VLVLDTDYKK, TPEVDNEALEKFDK,WENGECAEK [S-S] LAFNPTQLNGECHV, WENGECAEKK [S-S]LAFNPTQLNGECHV, SLAMAASDISLLDAQSAPLR, SLAMAASDISLLDAQSAPLR,VYVEELKPTPEGNLEILLQK, YLLFCMENSAEPEQSLACQCLVR,VAGTWHSLAMAASDISLLDAQSAPLR, VAGTWY	Chobert et al., 2005
		Cheese	VPPIPP	Butikofer et al., 2007
		Lactabumin	YGLF,YLLF	Sipola et al., 2002
		Ovalbumin	RADHPF	Matoba et al., 1999
		Casein	VPP, IPP	Nakamura et al., 2011; Jauhiainen et al., 2010; Ehlers et al., 2011
		Lactoferrin	LIWKL, RPYL	Fernandez-Musoles et al., 2014
		Egg	RVPSL	Yu et al., 2014
Anti-inflammatory	AS	Spirulina	LDAVNR, MMLDF	Vo and Kim, 2013
		Salmon	—	Ahn et al., 2012
	TP	Bean	LLSL, LSLL, NEGEAH,DNPIFSDHQ, NVLISSMEMKEGA	Oseguera-Toledo et al., 2011
	DE	Camel milk	MPVQAVLPFQEPVPDPVR	El Hatmi et al., 2016
		Egg	IRW, IQW	Huang et al., 2010; Majumder et al., 2013; Majumder et al., 2015

AS, TP, TA, and DE stand for aquatic sources, terrestrial plants, terrestrial animals, and dairy & eggs, respectively.
Uncommon amino acids are denoted by "X."

comes in handy in a few clinical situations and hematological studies (Koyama et al., 1998). Anticoagulants are predominantly important in prevention of ischemic events in patients with cardiovascular diseases (Rajapakse et al., 2005). Bioactive peptides, especially from marine resources, have been found to have anticoagulant activities (Koyama et al., 1998; Rajapakse et al., 2005; Jung et al., 2007; Jo et al., 2008; Jung and Kim, 2007, 2009). Antiplatelet peptides have also been found from natural resources; these peptides render their effect through inhibition of ADP-induced platelet aggregation and fibrinogen binding (Chabance et al., 1998).

Anti-diabetic effect

Diabetes mellitus (DM) is a very prevalent disease worldwide with higher level of outbreak in low- and middle-income nations. It is surmised that DM will affect 438 million people by 2030 (Yu et al., 2012). Therefore, scientific studies have been directed toward finding effective but cheaper solutions to cope with the problem. Bioactive peptides have been shown to exert anti-diabetic effect mainly through two ways: (1) insulin release (Srinivasan et al., 2013; Oseguera-Toledo et al., 2015); and (2) activity against α-glucosidase (Yu et al., 2012; Oseguera-Toledo et al., 2015; Zambrowicz et al., 2015), α-amylase (Yu et al., 2012; Oseguera-Toledo et al., 2015), and Dipeptidyl peptidase-4 (DPP-IV) (Oseguera-Toledo et al., 2015; Zambrowicz et al., 2015).

Srinivasan et al. (2013) found ten peptides from skin secretions of the tetraploid clawed frog *Xenopus laevis* with stimulatory effect on insulin release from the rat BRIN-BD11 clonal β cell line. They mentioned two peptides (CPF-7 and CPF-SE1; refer to Table 2 for their amino acid sequences) as the most potent stimulators of insulin release from the cell line (Srinivasan et al., 2013).

Yu et al. (2012) identified eight peptides from albumin with activity against α-glucosidase and α-amylase. They further reported that one of the peptides, KLPGF, had the highest effect against α-glucosidase and α-amylase with IC_{50} values of 59.5± 5.7 and 120±4.0 μmol·l^{-1}, respectively (Yu et al., 2012). Moreover, Zambrowicz et al. (2015) reported high level of anti-diabetic effects of bioactive peptides in a by-product of phospholipid extraction from egg yolk through inhibition of α-glucosidase and DPP-IV. They claimed that a peptide from the by-product, with amino acid sequence of LAPSLPGKPKPD, showed the strongest α-glucosidase inhibitory (1065.5 μmol·l^{-1}) and DPP-IV inhibitory (361.5 μmol·l^{-1}) activities (Zambrowicz et al., 2015).

Furthermore, three peptides from soy glycinin, with amino acid sequences IAVPGEVA, IAVPTGVA, and LPYP, were found to increase glucose uptake in human hepatic HepG2 cells. This effect was claimed to be via the stimulation of protein kinase B and adenosine monophosphate-activated protein kinase pathways stimulated by activation of two glucose transporters, i.e., GLUT1 and GLUT4 (Lammi et al., 2015).

Hypocholesterolemic and hypotriglyceridemic effects

Blood lipid profile was shown to be associated with bioactive peptides from different resources. In a study on the effect of fish protein hydrolysates prepared from flesh remnants on salmon bone frames after filleting, Wergedahl et al. (2004) found that fish protein hydrolysate (FPH) reduced plasma concentration of cholesterol in a hyperlipidemic animal model, i.e., the obese Zucker rat. They explained that this effect could not be through the excretion of fecal bile acids since dietary FPH did not affect the fecal bile acid; instead, they suggested that this effect of FPH could be by increasing hepatic activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. They also associated cholesterol regulatory effect of FPH to significant reduction of Acyl-CoA cholesterol acyltransferase (ACAT) activity (Wergedahl et al., 2004). A significant reduction of the plasma cholesterol concentration, especially the VLDL and LDL cholesterol concentrations, was also reported in rats fed a cholesterol-enriched diet by using papain-hydrolyzed pork meat (Morimatsu et al., 1996).

On the other hand, Kagawa et al. (1998) stated that reduction in serum triglycerides is even more important than decrease in serum cholesterol to prevent cardiovascular disease. The authors found a bioactive peptide, VVYP, from globin digest with a capability to rapidly clear dietary hypertriglyceridemia by inhibition of fat absorption from digestive tract and increased activity of hepatic triglyceride lipase (HTGL) (Kagawa et al., 1998).

Anti-anemic effect

Anemia can be caused by iron deficiency and therefore, chelating agents with ability of enhancing iron bioavailability can decrease the level of anemia. Lin et al. (2015) studied anti-anemic activity of protein hydrolysate prepared by enzymatic hydrolysis of beheaded and eviscerated hairtail in male Wistar rats and found that the hydrolysate could be regarded as a potential iron-delivery and anti-anemic source with no major disturbance in natural microbiome and gastrointestinal mucosa (Lin et al., 2015).

Furthermore, de la Hoz et al. (2014) revealed that enzymatic hydrolysis of the extract of sugar-cane yeast (*Saccharomyces cerevisiae*) by Viscozyme yielded iron-binding peptides, which increased iron bioavailability. They analyzed iron bioavailability through the iron dialyzability (i.e., the amount of soluble and stable iron until intestinal digestion) during in vitro digestion. They further isolated the peptides through immobilized metal affinity chromatography (IMAC) and showed that His, Lys, and Arg were more prevalent in these anti-anemic peptides (De la Hoz et al., 2014).

ACE inhibitory and antihypertensive effect

Hypertension is regarded as an important chronic health problem in epidemic proportions. It is considered a high risk factor for such complications as arteriosclerosis, stroke, myocardial infarction and end-stage renal disease (Jung et al., 2006).

One of the most considerable instruments in mammals in order to keep blood pressure homeostasis and fluid and salt balance is renin-angiotensin system. Angiotensin I converting enzyme (ACE) is a key factor in the mentioned system to regulate blood pressure. In other words, inhibition of this enzyme is very applicable method to control hypertension (Lee et al., 2010). ACE renders its effect by catalyzing formation of angiotensin II which is a vasoconstrictor (Nii et al., 2008). Synthetic inhibitors, such as captopril, enalapril, alacepril and lisinopril, are commercially available but their use is restricted due to

their possible adverse effects including cough, taste disturbances, and skin rashes (Lee et al., 2010). Therefore, special attention has been given to ACE inhibitory effects of nutraceuticals from bio-resources. Bioactive peptides from natural resources have been found to have a high level of ACE-inhibitory and antihypertensive effects (Je et al., 2005a, b, c; Jung et al., 2006; Nii et al., 2008; Lee et al., 2010; Yamamoto, 2010; Adje et al., 2011; Norris and FitzGerald, 2013; Singh et al., 2014; Mohanty et al., 2015; Capriotti et al., 2015; Esteve et al., 2015; El Hatmi et al., 2016). These peptides are very valuable because they have variety of functions and they are easily absorbed in the body and therefore, they can potentially be considered a great alternative for the synthetic antihypertensive drugs (Lee et al., 2010). Although a huge body of research has been dedicated to antihypertensive effect of bioactive peptides from plant (Motoi and Kodama, 2003; Chen et al., 2003; Motoi and Kodama, 2003; Nakano et al., 2006; Kodera and Nio, 2006; Kodera and Nio, 2006; Lee et al., 2006a, b; Zhu et al., 2006; Oseguera-Toledo et al., 2011; González-García et al., 2014; Oseguera-Toledo et al., 2015; Capriotti et al., 2015; Esteve et al., 2015; Coscueta et al., 2016; Da Silva Vaz et al., 2016), terrestrial animals (Morimatsu et al., 1996; Arihara et al., 2001; Nakashima et al., 2002; Saiga et al., 2003; Vercruysse et al., 2005; Arihara, 2006; Yu et al., 2006; Sentandreu and Toldra, 2007; Li et al., 2007; Chang et al., 2007; Wang et al., 2008a; Xu et al., 2009; Shimizu et al., 2009; Kim et al., 2009; Liu et al., 2010; Bernardini et al., 2012; Escudero et al., 2013), seafood (Jeon et al., 1999; Byun and Kim, 2001; Morimura et al., 2002; Ohba et al., 2003; Fahmi et al., 2004; Je et al., 2005; Je et al., 2005; Nagai et al., 2006; Hai-Lun et al., 2006; Padhi and Verghese, 2008; Wang et al., 2008b; Tsai et al., 2008; Nii et al., 2008; Lee et al., 2010; Lee et al., 2010), and dairy (Hernandez-Ledesma et al., 2004; Chen et al., 2007; Sagardia et al., 2013; Elfahri et al., 2014; Wada and Lönnerdal, 2014; Mohanty et al., 2015; Coscueta et al., 2016) products among others, serious efforts have not been allocated to make commercial use of these potentially potent antihypertensive peptides in developing countries. This may be due to various factors such as technological barriers, economic issues, lack of public awareness about the antihypertensive peptides, to name a few.

Anti-inflammatory effect

When the body is exposed to pathogen attacks or tissue injury caused by biological, chemical, and/or physical factors, inflammation occurs as a natural defensive mechanism. In this regard, macrophage-released inflammatory mediators such as nitric oxide (NO) and proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6, and -1β play pivotal roles to initiate defense reactions. However, overproduction of these inflammatory mediators can cause several ailments such as rheumatoid arthritis, asthma, atherosclerosis, and endotoxin induced multiple organ injury in humans (Ahn et al., 2012).

Bioactive peptides from different resources have been able to block inflammation (Nagaune et al., 1989; Huang et al., 2010; Ahn et al., 2012; Majumder et al., 2013a, b, 2015; Vo and Kim, 2013). This is very important because authors have recently warned about possible negative effects of synthetic drugs and therefore, foodstuffs with potential anti-inflammatory effects are in the first row of attention.

It is noteworthy that NO is regarded as an important signaling molecule in vasodilation, neurotransmission, and host immune defense (Ahn et al., 2012) and peptides from whey protein (Ballard et al., 2009), Aα-lactabumin and Aβ-lactabumin (Sipola et al., 2002), ovalbumin (Matoba et al., 1999), flaxseed protein (Udenigwe and Aluko, 2012), skeletal muscle protein (Takahashi et al., 2009), and even human casein (Fujita et al., 1996) were found to enhance NO production.

Effects on nervous system

An overview of reported effects of peptides on nervous system is given in Table 3.

Opioid and antinociceptive

Pharmacological management of various types of pain has gained a strong attention in recent years (Brantl et al., 1985). Opioids are known as drugs with direct effect to alleviate neuropathic pain and therefore, they can be considered as a potentially potent source of antinoceptive drugs (Nair et al., 2015). There has been a great concern regarding side effects of popular opioids such as morphine and codeine as to tolerance, addiction, hyperalgesia, abuse, and toxicity (Brantl et al., 1985).

By virtue of adverse effects of synthetic opioids on health, science has recently shifted its concentration on finding natural sources with antinoceptive effect. Interestingly, bioactive peptides from different resources such as wheat (Fukudome and Yoshikawa, 1993; Takahashi et al., 2000), camel milk (El Hatmi et al., 2016), and bovine blood (Brantl et al., 1989; Piot et al., 1992) were found to exert opioid effect. It is of great importance to know that these peptides are considered as opioid agonist-antagonist. In other words, they can have both agonist and antagonist effect. This is very imperative because as opioid agonists, they induce an analgesic effect, which is characteristically found in opioid ligands, whereas as opioid antagonists at the NK1 receptors, they block the signals induced by the pronociceptive peptides involved in pain signaling (Zhang et al., 2011). Furthermore, Huang et al. (2016) mentioned that the dynorphin/κ opioid (KOP) receptor system leads to adverse emotional conditions. When activated by selective agonists, the receptor system causes strong emotional consequences in humans and conditioned place aversion in animals (Huang et al., 2016). Therefore, opioid peptides from natural sources are very important due to their dual role as opioid agonist and antagonist. However, their application is still limited because of their varying influence on blood-brain barrier permeability, their sensitivity to metabolism inside the body, and lack of suitable delivery systems for them (Brantl et al., 1985).

Relaxing effect

Bioactive peptides from natural resources, especially milk and its derivatives, have been indicated to have relaxing effect. Historically, Miclo et al. (2001) mentioned that cow or human breast milk have tranquilizing effect because of their benzodiazepine-like molecules. They claimed that a peptide released by trypsin-mediated hydrolysis of α_{s1}-casein showed benzodiazepine-like effect (Miclo et al., 2001). A few years later, Messaoudi et al. (2005), also, reported that a tryptic hydrolysate from bovine milk α_{S1}-casein decreased stress level in the treated

Table 3. Effects of bioactive peptides on nervous system.

Effects	Origin		Amino acid sequence (in single-letter code)	Reference
Opioid and antinociceptive	TP	Wheat	GYYPT, YPISL	Takahashi et al., 2000; Fukudome and Yoshikawa, 1993
	TA	Bovine blood	YPWT, LVVYPWTQRF, VVYPWTQRF	Brantl et al., 1989; Piot et al., 1992
	DE	Lactabumin	YGLF,YLLF	Yoshikawa et al., 1986
		Bovine milk	YPFPGP,YPFPGPI	Boutrou et al., 2013
		Bovine /3-casein	YPFPGPI	Brantl et al., 1979
		Bovine milk-derived lactoferrin	—	Hayashida et al., 2003
		Kefir microorganisms on bovine milk	YPFPGPI, YPVEPF, YPSYGLN, YPFPGPIPN, YPFPGPIPNSLPQ	Dallas et al., 2016
		Camel milk	YFPIQFVQSR,YPSYGIN	El Hatmi et al., 2016
		Human milk	YVPFP, YPFV,YPFVE, YGLF	Kampa et al., 1996; Kostyra et al., 2004; Brantl, 1985
		Bovine milk-derived lactoferrin	—	Hayashida et al., 2003
		Milk-derived	—	Tsuchiya et al., 2006
		Human lactoferrin	—	Raju et al., 2005
Relaxing peptides	DE	Bovine Casein	YLGYLEQLLR, YLGYLEQ	Cakir-Kiefer et al., 2011; Messaoudi et al., 2005
		Bovine as1-casein	YLGYLEQLLR	Miclo et al., 2001; Hernández-Ledesma et al., 2014
		Bovine milk lactoferrin	—	Takeuchi et al., 2003; Kamemori et al., 2004
Anti-amnesic	AS	Tilapia	Many peptides have been introduced. Please refer to the related reference.	Huang et al., 2015a, b
		Shrimp waste	LFH	Li-Chan et al., 2016
		Anchovy	—	Su et al., 2016
	TA	Porcine cerebral hydrolysate	RILDWYKK, RVGSMEKART, RLSFDRVGSMEKA, RWALNEDQMATEKL, KRFGYETEVMGASFRN, KLISPFVGRILDWYKK, KSTGQDYAPADDPG VNSVRE, KKSTGQDYAPADDPGVNSVRE, RNKDEILELAGCDLLTIAPKL, KQFTTVVADSSDFDSMKSYQPRD, KLQQEGINCNMTLLFSFPQAVAAAKAKV	Zou et al., 2015
	TP	Defatted walnut meal	WSREEQEREE, ADIYTEEAGR	Chen et al., 2015

AS, TP, TA, and DE stand for aquatic sources, terrestrial plants, terrestrial animals, and dairy & eggs, respectively.

subjects compared to control subjects who only received placebo (Messaoudi et al., 2005). More recently, Zhao et al. (2016a, b) stated that peptide fractions isolated from protein hydrolysate of croceine croaker (*Pseudosciaena crocea*) swim bladder exerted anti-fatigue and relaxing effect in mice (Zhao et al., 2016a, b).

It is noteworthy that relaxing effect of peptides from bovine milk-derived α_{s1}-casein has long been emphasized; however, future studies are directed toward investigating this effect of peptides from other dairy and/or even nondairy sources.

Anti-amnesic

Amyloid beta (Aβ) is a proteolytic derivative of the large transmembrane protein amyloid precursor protein (APP) and it plays role in outbreak of Alzheimer Disease (AD). Aβ generation occurs in the presence of β-secretase. Therefore, inhibition of β-secretase can be a potentially effective way to control and prevent AD. A bioactive peptide, with the amino acid sequence of LFH, from shrimp waste with inhibitory activity against β-secretase was recently reported (Li-Chan et al., 2016).

Zou et al. (2015) claimed that bioactive peptides obtained from porcine cerebral hydrolysate have potential ability to protect against memory impairment caused by Pb^{2+} presumably by reducing the Pb^{2+} concentration of the blood and brain (Zou et al., 2015).

Moreover, Chen et al. (2015) examined the effect of defatted walnut meal hydrolysate on learning and memory in D-galactose-treated mice. They assumed that two peptides, i.e., WSREEQEREE and ADIYTEEAGR, from the hydrolysate are able to fight against memory and learning impairment in the mice.

Furthermore, in an in vitro study, Su et al. (2016) revealed that Anchovy (*Coilia mystus*) protein hydrolysate has therapeutic potential for memory deficit through inhibition of acetylcholinesterase (AChE). AChE is responsible for catalyzing hydrolysis of Ach into choline and acetic acid, which leads to reduction in acetylcholine (Ach) levels. Ach is a small-molecule neurotransmitter which regulates memory, concentration and consciousness (Su et al., 2016). Su et al. (2016) further followed up on their hypothesis in an in vivo trial on mice and stated that intervention by using the hydrolysate could improve spatial memory of scopolamine-impaired mice (Su et al., 2016).

Effects on gastrointestinal system

Table 4 presents an overview of reported effects of peptides on gastrointestinal system.

Anti-obesity

Obesity has turned into one of the most serious health problems in the current century and it is believed to elevate the probability of heart disease, type-2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis, among others (Micewicz et al., 2015). There has thus been a great deal of interest in anti-obesity drugs with satiating and appetite suppressant effects; however, the use of these drugs is limited due

Table 4. Effects of bioactive peptides on gastrointestinal system.

Effects		Origin	Amino acid sequence (in single-letter code)	Reference
Anti-obesity	TP	Soybean	LPYPR, VRIRLLQRFNKRS	Takenaka et al., 2000; Nishi et al., 2003
	DE	Milk	MAIPBTSZPGACVMILYFHKR	Beucher et al., 1994; Pedersen et al., 2000
	TA	Neuromedin U	XXFRPN	Micewicz et al., 2015
	AS	Blue whiting (*Micromesistius poutassou*) and brown shrimp (*Penaeus aztecus*)	—	Cudennec et al., 2008
Prebiotic	DE	Bovine whey protein	—	Ibrahim and Bezkorovainy, 1994
		Bovine lactoferrin	APRKNVRWCTISQPEWLECIRA	Oda et al., 2013
		Casein	—	Zhang et al., 2011; Prasanna et al., 2012
Protective effect on the gut mucosa	DE	Casein and lactalbumin	—	Claustre et al., 2002
		Whey protein	YLLF	Martínez-Maqueda et al., 2013a, b
		Casein	AYFYPEL, YFYPEL	Martínez-Maqueda et al., 2013a, b

AS, TP, TA, and DE stand for aquatic sources, terrestrial plants, terrestrial animals, and dairy & eggs, respectively.
Uncommon amino acids are denoted by "X."

to their adverse effects such as depression and cardiovascular risks (Ziauddeen and Fletcher, 2013). Therefore, science has shifted its focus on bioactive agents without or with minimum side-effects from natural resources.

One of the most noticed ways the bioactive agents render their anti-obesity effect is through influence on cholecystokinin (CCK) release; CCK is one of the major intestinal regulatory peptides (Beucher et al., 1994) and an important physiologic endocrine factor in appetite control (Nishi et al., 2003a, b). Beucher et al. (1994) showed that glycomacropeptide, i.e., glycosylated forms of caseinomacropeptide (CMP), released from dietary casein during gastric digestion has satiating effect in rats via stimulation of CCK release by intestinal cells. This finding is supported by the results of Pedersen et al. (2000), who concluded that dietary amount of CMP can stimulate pancreatic secretion through CCK release. Furthermore, Nishi et al. (2003b) indicated that a fragment of soybean β-conglycinin with amino acid sequence VRIRLLQRFNKRS is responsible for its anorexigenic effect by stimulating CCK release. In an in vivo study, they had previously shown that β-conglycinin peptone suppresses food intake in rats (Nishi et al., 2003a).

More recently, (Micewicz et al., 2015) revealed that NM4-C_{16}, a truncated/lipid-conjugated neuromedin U (NmU) analog, has strong appetite suppressing effects in a diet-induced obese (DIO) mouse model; it is noteworthy that Neuromedin U (NmU) is an endogenous peptide with various physiological effects.

Prebiotic effects

Although most prebiotic agents promoting the growth and viability of probiotics like *Bifidobacterium* and *Lactobacillus* genera are currently nondigestible oligosaccharides (Yu et al., 2016), bioactive peptides and proteins from various resources have been considered for their effects on probiotics. In one of the earliest attempts to find prebiotic effect in nonfiber products, Ibrahim and Bezkorovainy (1994) reported that α-lactalbumin and β-lactoglubin had potent growth promoting influence on the probiotic *Bifidobacterium Iongum*. More recently, a prebiotic peptide from pepsin hydrolysate of bovine lactoferrin was found to exert bifidogenic effect (Oda et al., 2013).

Zhang et al. (2011) fractionated five casein hydrolysates produced by five different proteases and found that the >3000 kDa fractions were essential for stimulation of *Lactobacillus bulgaricus* and *Streptococcus thermophiles*. They further analyzed the total amino acid profiles of the ultra-filtered fractions and revealed that the hydrophilic amino acid residua including His, Lys, Glu and Ser are favorable for the prebiotic effect of the hydrolysates.

Protective effect on the gut mucosa

There is a protective viscoelastic mucous gel layer covering the luminal surface of the gastrointestinal tract. The layer, which is also termed as "gut barrier" (Moughan et al., 2013), is considered a barrier against the noxious luminal environment (Corfield et al., 2000). Mucosal tissue damage in parts of gastrointestinal tract might bring about the so-called inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease (Sluis et al., 2006). The main component of mucus layer is polymeric glycoproteins called mucins, which cover the epithelium of the gastrointestinal tract and epithelia in mammals (Montagne et al., 2004). Mucins are synthesized and secreted by specialized cells in intestinal epithelium, called goblet cells. In healthy mammas, there is a dynamic balance between mucin release by goblet cells and mucin loss through physical and proteolytic processes (Martínez-Maqueda et al., 2013a, b). In addition to internal factors such as hormones and cytokines, dietary regulation of mucin secretion has also been mentioned (Morel et al., 2003; Burger-van et al., 2009; Moughan et al., 2013).

In a study to determine effects of peptides derived from dietary proteins on mucus secretion, Claustre et al. (2002) revealed that two protein hydrolysates obtained by enzymatic hydrolysis of casein and lactalbumin prompted mucin release in rat jejunum. Later, Martínez-Maqueda et al. (2013a, b) found that two

peptides derived from casein hydrolysate induce mucin production in human intestinal cells.

In vitro vs. in vivo effects

Bioactive peptides and protein hydrolysates from different sources have shown a very large number of beneficial effects. However, a majority of the studies have launched in vitro experiments to show the effects. Although there were a few in vivo studies on the effect of the peptides and hydrolysates using animal models, it seems that there is still a research gap in analyzing the effect of these peptides and hydrolysates in humans when applied as functional foods and/or nutraceuticals. Therefore, in addition to in vitro and in vivo studies using animal models, future investigations should be directed toward evaluation of the effects of bioactive peptides-enriched functional foods and nutraceuticals in humans. Needless to say, such studies demand interdisciplinary efforts in which nutritionists, food science experts, animal science experts, physiologists, medical researchers, biotechnologists, etc., should contribute in unison.

Functional and antioxidant properties

Functional properties

Several functional properties have been reported for protein hydrolysates. It is known that the specificity of the enzyme, degree of hydrolysis (DH) and bulk density of the proteins influence the functional properties of the hydrolysates (Multilangi et al., 1996; Chobert et al., 1996; Kristinsson and Rasco, 2000). The specificity of the enzyme influence amino acid residues and both DH and bulk density of the proteins influence the length of the peptides. The DH needs to be controlled to avoid excessive hydrolysis that can impair functionality and cause unfavorable effects of the produced hydrolysates (Mune, 2015). The functional properties discussed below are universal and not specific for whether the peptides are from fish, milk or vegetables, but depends on the origin of the protein.

Solubility

In general, solubility of hydrolysates is expected to increase with increased DH due to an increment in low molecular weight peptides and ionic groups during hydrolysis (Mutilangi et al., 1996, Chobert et al., 1988a, Kristinsson and Rasco, 2000). Additionally, the balance of hydrophilic and hydrophobic forces of peptides is also mentioned as an important cause of solubility enhancement (Kristinsson and Rasco, 2000; Gbogouri et al., 2004). Several reported studies have also confirmed that increasing DH increases solubility of protein hydrolysates (Quaglia and Orban, 1987; Chobert et al., 1988a, b; Mutilangi et al., 1996; Linarès et al., 2000; Gbogouri et al., 2004; Klompong et al., 2007; Souissi et al., 2007; Balti et al., 2010; Geirsdottir et al., 2011). The solubility of the hydrolysates is especially improved at the proteins isoelectric point, pI (Chobert et al., 1988b).

Emulsifying properties

Emulsifying properties of hydrolysates are directly connected to their surface properties and are influenced by the extent of hydrolysis and enzyme treatment (Kristinsson and Rasco, 2000). This is due to the changes in molecule size, charge and distribution of hydrophilic and hydrophobic parts. Hydrolysates are surface active due to their hydrophilic and hydrophobic functional groups, and can absorb to an interface and thus work as an emulsifier. Whether hydrolysates improve the emulsifying properties more than the native proteins do is not certain. Reported results for emulsion capacity and stability do not show any clear trend due to different DH and enzyme treatment for the obtained hydrolysates. Different emulsifying properties of the hydrolysates have been reported. Some studies showed improved emulsion properties (Chobert et al., 1988b; Turgeon et al., 1991; Balti et al., 2010) whereas others showed that hydrolysates had decreased emulsifying properties compared to those of the native protein (Lee et al., 1987; Chobert et al., 1988a; Mutilangi et al., 1996; Klompong et al., 2007; Souissi et al., 2007; Taheri et al., 2014; Mune, 2015; Zou et al., 2016). The lack in improved emulsifying properties may be caused by too high DH of the hydrolysates. In order to retain or improve the emulsifying properties of hydrolysates over the native proteins, the extent of hydrolysis has to be carefully controlled. Low DH is recommended, since extensive hydrolysis results in a drastic loss of emulsifying properties (Kristinsson and Rasco, 2000; Gbogouri et al., 2004; Taheri et al., 2014; García-Moreno et al., 2017). High DH leads to smaller peptides, which are not able to form a stable film surrounding the fat globules (Lee et al., 1987; Chobert et al., 1988a). This is due to lack of unfolding and reorientation of smaller peptides compared to larger peptides (Gbogouri et al., 2004).

Foaming properties

As for the emulsifying properties (section 3.2.2), foaming properties are connected with the surface activity of the hydrolysates (Kristinsson and Rasco, 2000). Thus, the factors relevant to foaming are similar to those required for emulsification. Foam capacity of proteins can be improved by making them more flexible (hydrolysis) and exposing more hydrophobic residues for the adsorption at the air-water interface (Multilangi et al., 1996). Several studies showed decreased foaming stability for protein hydrolysates compared to that of the untreated proteins (Linarès et al., 2000; Klompong et al., 2007; Souissi et al., 2007; Mune, 2015; Zou et al., 2016). Some studies, on the other hand, reported increased foaming capacity of hydrolysates compared to untreated proteins (Kuehler and Stine, 1974; Balti et al., 2010; Mune 2015). An increment in foam capacity due to limited hydrolysis is attributed to more air incorporated into solution of small peptides due to rapid diffusion of peptides to the air-water interface (Kuehler and Stine, 1974; Mune 2015). However, small peptides do not have the strength required to form stable foams. Thus, high DH has a negative influence on the foaming stability (Kristinsson and Rasco, 2000).

Gelling properties

Gelation is favored by large molecules of proteins since they form extensive networks by cross-linking in three-dimensions (Wang and Damodaran, 1990, Jeewanthi et al., 2015). On the other hand, the structure of the proteins is altered during hydrolysis since buried hydrophobic groups are exposed and free to interact. It is proposed that noncovalent interactions,

mainly electrostatic and hydrophobic, are major interacting forces since they promote aggregation and subsequent gel settings (Fuke et al., 1985, Otte et al., 1996, Otte et al., 1997, Jeewanthi et al., 2015). However, Kuipers et al. (2005) concluded based on their findings that the aggregation is not a simple balance between repulsive electrostatic and attractive hydrophobic interactions, but much more complex. Gelling properties are observed both with limited hydrolysis (Ju et al., 1995; Otte et al., 1996; Kuipers et al., 2005) and more extensive hydrolysis, DH > 15% (Doucet et al., 2001).

Water holding capacity (WHC)

Hydrolysis of proteins affects the ability of the formed hydrolysates to adsorb and bind water. A linear relationship between amounts of certain amino acids and WHC has been observed for fish protein hydrolysates. Decreasing amount of glycine, arginine, alanine, hydroxyproline, and sum of hydrophobic amino acids increased the WHC (Šližytė et al., 2005). Moreover, WHC of hydrolysates increased with increasing DH. During enzymatic hydrolysis, the presence of polar groups (–COOH and –NH2) increases, and it is assumed that this has a substantial effect on the increased WHC observed for hydrolysates (Balti et al., 2010). However, others stated that the DH did not affect the WHC (Geirsdottir et al., 2011). Additionally, Choi et al. (2009) observed higher WHC of the insoluble fraction of protein hydrolysates than the soluble fraction.

Fat absorption capacity (FAC)

The mechanism of fat absorption capacity (FAC) is attributed to the physical entrapment of oil in a protein network. Some studies have shown no effect of DH on the FAC (Amiza et al., 2012) or no correlation between DH and FAC (Souissi et al., 2007). Other studies reported improved FAC of hydrolysates at low DH and that further increment in DH significantly decreased FAC (Geirsdottir et al., 2011; Gbogouri et al., 2004; Balti et al., 2010; García-Moreno et al., 2017). Low DH could even improve the FAC over the native protein (Balti et al., 2010, Mune, 2015). These observations could be explained by hydrolysis, which can liberate some peptides from the native protein, which would enhance the flexibility of the hydrolysates. The extensive hydrolysis would break many peptide bonds, thus contributing to the decrease of FAC (Souissi et al., 2007; Balti et al., 2010). As observed for the WHC, the FAC was higher for the insoluble fraction of protein hydrolysates than the soluble fraction (Choi et al., 2009). However, the opposite has also been observed (Yin et al., 2010). The different observations may be due to different DH of the soluble fraction, thus, different molecular sizes of the peptides.

Mineral binding

Bioavailability of minerals can be improved in the presence of hydrolysates due to increased mineral solubility. It is reported that hydrolysates can exert binding activity towards different minerals such as calcium (Jung and Kim, 2007, Huang et al., 2011, Chen et al., 2014), iron (Chaud et al., 2002; Lee and Song, 2009a), copper (Eckert et al., 2014), and zinc (Eckert et al., 2014). Different molecular sizes of the mineral binding peptides ranging from 1 to 1.5 kDa have been reported (Jung and Kim, 2007; Lee and Song, 2009b; Chen et al., 2014). However, Huang et al. (2011) observed highest binding affinity (calcium) with the lowest molecular weight fraction (<1 kDa).

Antioxidant properties

Oxidation processes have detrimental effects on human health and food quality. In the body, oxidants cause damage of lipid membranes, structural proteins and DNA which leads to degenerative diseases such as cancer, immune system decline, cardiovascular diseases as well as the aging process (Shahidi, 2015). In food, lipid oxidation, which is catalyzed by heat, light, enzymes or metals, leads to the formation of off-flavors and odors which negatively affects food function and nutrition. Moreover, food quality is further degraded by co-oxidation of proteins and vitamins (Schaich, 2016). Due to the potential health hazards of synthetic antioxidants (e.g., butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), and tertiary butylhydroquinone (TBHQ)), the employment of natural antioxidants has gained an increasing interest (Shahidi and Zhong, 2015). Peptides have been reported to exhibit antioxidant activity due to their properties to scavenge free radicals, donate electrons and/or chelate metals (Aluko, 2015). As for other bioactivities, peptides size, amino acid composition and structure are the factors affecting the ability of the peptides to inhibit oxidation (Sarmadi and Ismail, 2010). Particularly important is the presence of hydrophobic amino acids (e.g., A, L, V, G, P, F) which favors peptide interaction with lipids resulting in an enhanced radical scavenging activity. Similarly, the presence of electron donors (e.g., E, M, N) and amino acids exhibiting chelating activity (e.g., D, E, H, W) also increases the antioxidant activity of the peptides (Aluko, 2015). Comprehensive reviews have been published on the production of antioxidant peptides from proteins of different origin such as: i) aquatic resources (e.g., algae, oysters, mussel, sardine, bonito, tuna, mackerel, yellowfin sole, hok, squid, salmon, eel, round scad, tilapia, channel catfish, horse mackerel, monkfish) (Samaranayaka and Li-Chan, 2011; Wu et al., 2015a, b; Sila and Bougatef, 2016), ii) terrestrial plants (e.g., wheat, corn, rye, kamut, spelt, rapeseed/flaxseed, rice, soybean, cacao seeds, hempseed, pea) (Malaguti et al., 2014; Aluko, 2015; Rizzello et al., 2016), iii) terrestrial animals (e.g., porcine myofibrils, dry-cured ham, buffalo horn, porcine skin) (Mora et al., 2014), iv) dairy (bovine, ovine, buffalo and human milks, whey protein) (Power et al., 2013; El-Salam and El-Shibiny, 2013; Brandelli, et al., 2015), and v) eggs (e.g., egg white ovalbumin, egg white lysozyme, egg yolk) (Yu et al., 2014; Nimalaratne and Wu, 2015). Most studies evaluated the antioxidant activity of the hydrolysates/peptides in vitro using different methods such as DPPH scavenging activity, reducing power, ABTS scavenging activity, Fe^{2+} chelating activity, β-carotene bleaching preventing activity, linoleic acid autoxidation inhibition activity (Chalamaiah et al., 2012). Some studies also investigated the ability of the hydrolysates/peptides to inhibit lipid oxidation in real food systems such fish oil in water emulsions (Farvin et al., 2014; García-Moreno et al., 2016; Ghelichi et al., 2017) or fish oil microcapsules (Tamm et al., 2015; Morales-Medina et al., 2016). Finally, only a few works are devoted to studying the antioxidant activity of peptides in cell-based and in vivo systems (Chakrabarti et al., 2014).

Commercial applications of bioactive peptides and hydrolysates

Many of the bioactive peptides mentioned in this review and previously reported studies occur naturally in several traditionally consumed foods (e.g., fermented foods) or during biological processes inside the human body (e.g., enzymatic reactions). Nevertheless, bioactive peptides and hydrolysates have recently been added to numerous products gaining the name "functional foods" and "nutraceuticals." Besides, bioactive peptides and hydrolysates are used to produce drugs as well as cosmetics and health-promoting products (Hartmann and Meisel, 2007). Table 5 represents examples of commercially available products in which bioactive peptides and protein hydrolysates from different sources have been used.

Despite the recent surge in manufacture of commercial products using bioactive peptides and hydrolysates, industries seem not to be at the cutting edge of this sector of biotechnology. In other words, although there have been virtually uncountable number of scientific investigations on functionality and bioactivity of peptides and hydrolysates derived from natural sources, very few of the findings have been operationalized in industry. This might be due to several factors including high operational and set-up costs, sensory concerns, low market acceptability on account of uncertainty upon manufacturers' claims and potential side effects, unsatisfactory return on invested capital, legislative and religious issues in some countries, and unaffordability of the products for the public. Likewise, Li-Chan (2015) listed a few challenges in commercialization of nutraceuticals and functional foods containing bioactive peptides as follows: (i) complications in methodology for quality assurance; (ii) sparse data on bioavailability and metabolic fate; (iii) inadequate clinical evidence of bioefficacy; and (iv) bitterness of peptides (Li-Chan, 2015). In addition, when considered to be added as antioxidant agents in food systems, bioactive peptides and hydrolysates should meet a few demands; they should be affordable and competitive with synthetic antioxidants, not cause toxicity in human body, be effective at low concentrations, be able to tolerate processing operations and be stable in the finished products, and present favorable organoleptic properties (Sila and Bougatef, 2016).

Challenges and concerns in application of bioactive peptides and hydrolysates in different industries may also depend on the source(s) from which the peptides and hydrolysates are obtained. Harnedy and FitzGerald (2012) named large-scale production, compatibility with various food matrices, gastrointestinal stability, bioavailability, and long term stability as the main concerns in manufacture of functional foods containing bioactive peptides or protein hydrolysates with marine origins (Harnedy and FitzGerald, 2012). Additionally, Lafarga and Hayes (2016) stated that peptides and hydrolysates from casein and whey proteins might cause allergy in some consumers (Lafarga and Hayes, 2016). Korhonen (2009) indicated that milk-derived proteins, e.g., casein and whey, are the most prevalent source of functional foods and nutraceuticals containing bioactive peptides; however, production of commercially available products from these sources have been restricted by lack of suitable large-scale technologies; he suggested that nanofiltration and ultrafiltration techniques can be adopted to overcome technological barriers to make industrial and commercial use of bioactive peptides from milk proteins (Korhonen, 2009). Udenigwe and Rajendran (2016) uttered that the most notable hindrance in commercialization of functional foods containing plastein is the costs levied by high price of enzymes required for plastein reaction (Udenigwe and Rajendran, 2016). Grienke et al. (2014) pointed to the necessity of collaboration between academia and industry to reach a win-win condition to exploit favorable bioactive peptides from mussel meat and incorporate them in functional foods; however, they presumed that challenges such as stability, bitterness, and lack of appropriate food-grade formulation procedures account for the current gap from lab beakers to factory batches. They further shed light on the importance of interdisciplinary expertise in order to the development of functional foods, food ingredients, or pharmaceuticals from mussels (Grienke et al., 2014).

Another bottleneck in application of bioactive peptides and hydrolysates is the lack of scientific studies on the effects of peptides on humans. Although there have been several in vivo investigations proving the bioactivity of peptides and hydrolysates in

Table 5. Examples of commercially available products from bioactive peptides and hydrolysates.

Product	Source	Claimed application	Type of fraction	Manufacturer
Lactium®	Milk	Relaxing	Peptide (YLGYLEQLL)	Ingredia, Arras Cedex, France
Myprotein™	Whey	Sport nutrition	Whole hydrolysate	The Hut, Ltd, UK
Sato Marine Super P	Sardine	Antihypertensive	Peptide (VY)	Sato Pharmaceutical Co., Ltd., Tokyo, Japan
Hyvital®	Whey or casein	Infant nutrition	Whole hydrolysate	FrieslandCampina, Netherlands
Proyield®	Nonanimal protein (soy, cotton seed, wheat, pea)	Biopharmaceutical cell culture media	Whole hydrolysate	FrieslandCampina, Netherlands
Stedygro®	Protein from casein, soy, malt, gelatin, and cotton	Microbial culture media	Whole hydrolysate	FrieslandCampina, Netherlands
Lacprodan®	Protein from casein and whey	Sport nutrition and beverage	Whole hydrolysate	Arla Foods Ingredients, Denmark
Ameal S	Milk casein	ACE inhibition	Peptides (IPP and VPP)	Calpis, Japan
Vasotensin®	Bonito	Anti-hypertension	Peptide (LKPNM)	Metagenics, US
Peptide Nori S	*Porphyra yezoensis*	Anti-hypertension	Peptide (AKYSY)	Riken Vitamin, Japan
Stabilium® 200	Fish	Relaxing	Whole hydrolysate	Yalacta, France
Seishou-sabou	Bovine and porcine blood	Anti-obesity	Peptide (VVYP)	Moringa & Co., Ltd., Japan
Marine peptide	Sardine	ACE inhibition	Peptides	SenmiEkisu, Japan
BioZate	Whey	Anti-hypertension	Peptides	Davisco Foods, US
NOW®	Whey	Sport nutrition	Whole hydrolysate	NOWfoods, US
Nutripeptin™	Cod	Hypotriglyceridemic	Whole hydrolysate	Nutrimarine Life Science AS, Norway
VERISOL®	Collagen	Anti-aging	Peptides	GELITA Inc., US
Remake CholesterolBlock	Soy protein	Hypocholesterolemic	Peptide (CSPHP)	Kyowa Hakko, Japan

animal models, the results of these studies cannot be confidently generalized to humans due to the disagreement between human and animal studies. Nongonierma and FitzGerald (2016a) explained that the discrepancy between human and animal studies could be caused by two major reasons, i.e., biological differences between humans and animals and differences in experimental set-up (Nongonierma and FitzGerald, 2016b).

In addition to their application in functional foods and nutraceuticals, bioactive peptides and hydrolysates are used to produce drugs and cosmetics. Bioactive peptides are prioritized as drugs over proteins and antibodies since they have a higher capability of penetration into tissues by virtue of their smaller size. Furthermore, peptides with therapeutic effects are commonly less immunogenic than recombinant proteins and antibodies (Vlieghe et al., 2010). However, peptide-based drugs industry encounters operational logjams such as physical and chemical instability, short in vivo half-lives, and low oral bioavailability; interestingly, a portion of these logjams can be broken by encapsulation of the drugs in order to improve their stability and bioavailability (Kadam et al., 2015). Furthermore, use of antimicrobial peptides in drug industry has been limited to topical applications to cure surface infections, whereas parenteral and oral applications of these peptides are strongly restricted due to such factors as toxicity. However, recent developments like fully synthetic peptides and peptidomimetics (i.e., synthetic molecules mimicking peptides) have opened new avenues in order to rid peptide-based drug making industry of the technological obstacles (Vlieghe et al., 2010; Narayana and Chen, 2015). On the other hand, natural bioactive peptides have gained more attention in cosmetics industry rather than drug making, which is justifiable since cosmetics are consumed topically and therefore, toxicity of natural peptides in systemic applications is a minor concern when it comes to the production of natural-peptide-based cosmetics. Bioactive peptides have been specifically emphasized in skincare and cosmetic dermatology because of their ability to stimulate collagen and render botox-like anti-wrinkle effect (Fields et al., 2009).

To sum up, there is still a long way to be paved to make use of bioactive peptides from natural resources in the so-called peptide-based products. In recent years, more and more companies have inclined toward manufacture of functional foods and nutraceuticals from bioactive peptides and hydrolysates although it seems that these products have not gained widespread publicity, yet. This might in general be caused by two main factors, i.e., technological hurdles and high price of these products in the market. Nevertheless, functional foods and nutraceuticals, reportedly, account for the major portion of products based upon bioactive peptides and hydrolysates from natural sources. Moreover, medicinal applications of these peptides have been restricted to topically used products because of concerns over toxicity of the peptides when applied systemically. Of course, alternative technologies such as fully synthetic peptides and peptidomimetics have been proposed to overcome these problems. However, there has been a recent spark in production of anti-aging cosmetics based on bioactive peptides from natural resources with appropriate level of market acceptance.

Conclusion

Protein hydrolysates have been produced from variety of sources with plant and animal origins through chemical, enzymatic, and microbial procedures. Each of these methods have their own cons and pros but they all share a common disadvantage in terms of the bitter taste of final products that limit their applications. Different methods have been proposed to reduce bitterness of the peptides. Despite a few optimistic findings, no single method has been presented to fully remove the bitter taste of the peptides to be economical in industrial scales. A recent trend in this regard is the characterization and purification of peptides with stronger and more specific effects. The peptides have shown different effects on immune, cardiovascular, nervous, and gastrointestinal systems. They have also been found to exert functional and antioxidant properties in food systems. In spite of the recent interest in production of peptide-based foods, nutraceuticals, and pharmaceuticals in commercial scale, there is still a gap between wide academic findings and commercialization of bioactive peptides from natural resources.

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