Research Inventy: International Journal of Engineering And Science
Vol.9, Issue 1 (Jan 2019), PP -40-51
Issn (e): 2278-4721, Issn (p):2319-6483, www.researchinventy.com

A Scoping Review on Bioactive Peptides from Meat and Some Daily Food and Their Role in Human Health and Nutrition

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ABSTRACT*: The objective of the proposed review was focused in studying bioactive peptides from daily foodsand their role on human health and nutrition. Itoffers major potential for incorporation into functional foods and nutraceuticals.Itcan be derived from plant and animal origin. Methods of producing peptidesare occurred in the proteolytic digestion of parent proteins, plant and bacterial proteases. It has physiological effect on the main body systems.There are some challenges in bioactive peptides such as fermented productscompared to the raw materials could change in amino acid composition, size andsequence of the peptides.It is obvious that these peptides can be used for health promotion and disease risk reduction, especially because they have some advantages compared to synthetic drugs.*

Key words: *functional food, animal origin,bioactive peptides, bioactivities, productionhuman health and nutrition*

Date of Submission: 15-08-2019 Date of Acceptance: 29-08-2019

I. INTRODUCTION

Peptides areconsidered as proteins formed in the cell within large prepropeptides forms, which can lead to active products. Bioactive peptidesact as a main role inphysiological functions and pathogenesis. They have been defined as food derived componentsthat can lead toseveral effects in the body. Bioactive peptides can be absorbed through small intestine where theyenter through the circulatory system to do various physiological effects, or they make some othereffects in the digestive tract (Lafarga et al., 2016).

Protein hydrolysates and peptides from natural resources can be used as functional foodsor as technological components. The functional products may include the whole hydrolysatewith purified peptides (Lafarga et al., 2016). Peptides with different effects might be derived from a monohydrolysate. So, sometimes additional stages are required in order to incorporate peptideswith intended effectsin the final product. This isolation process is carried out by controlling the process of enzymolysis (Zou et al., 2016).

The objective of the proposed review was focused in studying bioactive peptides from daily foodsand their role on human health and nutritionwith providing a comprehensive overview of the activities that have been reported for protein hydrolysates from various protein sources.

Sources Of Peptides And Production

History of Bioactive Peptide Discovery

Bioactive peptide discoveries have increased considerably since 1959, focusing on the identification of bioactive peptides from milk proteins. Historically, the first derived bioactive peptide wasconsideredin 1950 when Mellanderpublished that casein phosphorylated peptides has enhanced vitamin D-independent bone calcification in rachitic infants(Lafarga et al., 2016;Zou et al., 2016; Micewicz et al., 2015).

Bioactive Peptidesin food processing

Meat is considered a high-quality protein which it can represent the mostwidely investigatedsource for separating in a closing system of bioactive peptides. Table 1 shows different mechanisms for bioactive peptide

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generation. Calpains and cathepsinsendogenous enzymesarethe key process that affects the de-structuration ofproteins and release of a large number of peptides and free aminoacids.

In a recent study, Bauchartet al.（2017）havefound an increase of bioactive peptides inmeat after two weeks of storing than in fresh meat. Fu et al（2017）has indicated that storing meat can generate bioactive peptides in muscles after 20 days of extensive proteolysiswhich can be driven by oxidation processes. Zhang et al, (2013) have mentioned that oxidationprocess can regulate the endogenous enzymatic activity. Korhonen et al (1998) and Leygonie et al (2012) have indicated that changing of temperature and pH can affect the content of bioactive peptidesduring meat storage. Pihlanto et al (2015) has mentioned thatduring gastrointestinal proteolysis,ingested meat-derivative proteins are attacked by digestive enzymes secreted in the smallintestine. It should be stimulatedto generate peptides similar to one releasedin a physiological digestion process.Vercruysse et al, (2005) have indicated that enzymatic hydrolysis is a famous method selected to produce bioactive peptides products.

Table 1.Schematic representation of processes for obtaining meat bioactive peptides.

Product	Process	Carrier/Regulation	Functionality	Peptide Sequence	Reference
Meat	Proteolysis, oxidation	Endogenous enzymes	ACE-I activity	APPPPAEVPEVHEEVH, PPPAEVPEVHEEVH, IPITAAKASRNIA, LPLGG, FAGGRGG, APPPPAEVP	Bauchart et al 2017
Collagen	Enzymatic hydrolysis	Bacterial collagenase, exogenous enzymes, protease from Aspergillus oryzae	ACE-I and antioxidant activity	AKGANGAPGIAGAPGFPGAR GPSGPQGPSGPP, PAGNPGADGQPGAKGANGAP , GAXGLXGP, GPRGF, VGPV, QGAR, LQGM, LQGMH, LC	Arihara et al 2006
Cured products	Proteolysis	Endogenous enzymes	Antioxidant activity	DSGVT, IEAEGE, EELDNALN, VPSIDDQEELM,DAQEKLE, ALTA, SLTA, VT,SAGNPN	Fu 2017
Fermented products	Proteolysis	Presence of starter cultures	Antioxidant activity	FGG, DM	Escudero et al 2013

Xu et al. (2015) havereported that theamounts of essential amino acids hasincreased rapidlyinfermentation of soybean. Kleekayai et al. (2015) has identified twopeptides (SV and IF) and one antioxidant peptide (WP) from fermented shrimp. Pan et al. (2005)hasobtained two antihypertensive peptides with amino acidsequences of VPP and IPP from skimmed milk hydrolysatedigested by cell-free extract of Lactobacillus helveticus.

Production of Bioactive Peptides

Many published works have described the isolation of bioactive peptides following bacterial fermentation of milk and meatproteins. However, microbial fermentation of meat proteins has been less successful.Methods arebased on enzymatic hydrolysis which can lead to an advantage becausethey are more predictable tothe end products. Enzymes can be taken from plants, microorganisms or animals, and can be used alone or mixed with other enzymes. It is important that isolation of peptides by enzymatic hydrolysis is performed under certainconditions of such as temperature, pH, time taken, etc.

The production of bioactive peptides by enzymatic hydrolysis is shown in Fig1.The fractionation; purification and identification of bioactive peptidesare taking part in the procedure.

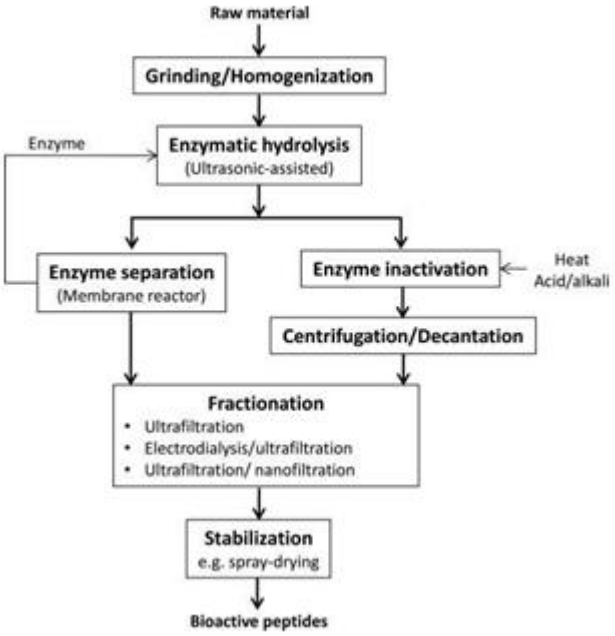

Figure 1. Flow diagram for the production of bioactive peptides.

Bioactivity Of Peptides

Bioactive Peptides on Immune System

An overview of reported effects on immune system is given in Table 2, which also shows the suggested peptides responsible for the effects.

Table 2.Effects of bioactive peptides on immune system.

Effects	Origin	Amino acid sequence (in single-letter code)	Reference
Antifungalpeptides	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 (Mytilusedulis)	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
	Mushroom	AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN, ATRVVYCNRRSGSV VGGDDTVYYEG, AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN	Wang and Ng, 2004; Lam and Ng, 2001
	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
	Venom of the social wasp (Polybiapaulista)	ILGTILGLLKSL	Wang et al., 2016
Antimicrobialpeptides	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	Cuthbertson et al., 2002;

Table 2. Effects of bioactive peptides on immune system (continued).

Effects	Origin	Amino acid sequence (in single-letter code)	Reference
Antimicrobialpeptides	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
	Zebrafishphosvitin	—	Ding et al., 2012
	Tegillarcagranosa hemoglobin	PSVQDAAAQISADVKK, VLASLNFGDR,ISAAEFGK, ISAEAFGAINEPMK, GHAITLTYALNNFVDSLDDPSR, MGSYYSDECAAAWAALVAVVQAAL, LNGHGLTLWYGIQNFVDQLDNADDLEDVARK	Bao et al., 2016
	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 Polybiapaulista	ILGTILGLLKSL,IDWKKLLDAAKQIL	Souza et al., 2005
	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	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
	Mushroom	AGTEIVTCYNAGTKVPRGPSAXGGAIDFFN	Lam and Ng, 2001
	Bean	KTCGNLANQYYPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCTK	Lin et al., 2010
	Frog skin	ALWMTLLKKVLKAAAKAALNAVLVGANA	Bergaoui et al., 2013
Immunomodulatory peptides	Atlantic salmon (Salmosalar)	—	Opheim et al., 2015
	Muscadomestica larvae	—	Sun et al., 2014
	Chlorella vulgarian	—	Morris et al., 2009
	Zebrafishphosvitin	—	Ding et al., 2012

Table 2. Effects of bioactive peptides on immune system (continued).

Effects	Origin	Amino acid sequence (in single-letter code)	Reference
Immunomodulatory peptides	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
	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
	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
Cytomodulatorypeptides	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 peptides	Bean (Phaseolus vulgaris L.)	KTYENLADTYKGPYF TTGSHDDHYKNKEHLRSGRMRDDFF, KTCGNLANQYYTPCFTTSNCDDHCKNKEHLRSGRCRDDFRCWCTK, KTYENLADTYKGPYFTTGSHDDHYKNKEHLRSGRYRDDFF	Wang and Ng, 2007; Lin et al., 2010; Wu et al., 2011
	Mushroom Flammulinavelutipes	—	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
	Frog skin	IKLSPETKDNLKKVLKGAIKGAIVAKMV, GLWSKIKEAAKAAGKAALNAVTGLVNQGDQPS, GLVG TLLGHIGKAILG,GLVGTLLGHIGKAILS	Attoub et al., 2013; Conlon et al., 2007; Mechkarska et al., 2014; Conlon et al., 2014
	Sea hare (Dolabellaauricularia)	XVXXX	Madden et al., 2000; Pettit et al., 1998; Turner et al., 1998; Vaishampayan et al., 2000
	Muscadomestica larvae	—	Sun et al., 2014
	Fish sauce	—	Lee et al., 2003, 2004
	Sea hare (Dolabellaauricularia)	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
	Bovine Milk	VENLHLPLPLL,NLHLPLPLL, ENLHLPLPLL, ALNENLLRFFVAPFP EVFG, LNENLLRFFVAPFPEVFG, NENLLRFFVAPFPEVFG, ENLLRFFVAPFPEVFG, FVAPFPEVFG	Juillerat-Jeanneret et al., 2011
Antimutagenic andantigenotoxic peptides	Kefir	—	Guzel-Seydim et al., 2011
	Bovine plasma, globulin and albumin	—	Park and Hyun, 2002
	Silk fibroin	—	Park et al., 2002

Bioactive Peptides onNervous System

An overview of reported effects of peptides on nervous system is listed in Table 3.Brantl et al.(1985)have reviewed the pharmacological management of various types of pain in the most recent years. There is also a great concern related to the side effects of opioids such as morphine, codeine, addiction, hyperalgesia, abuse, and toxicity (Nair et al., 2015; Brantl et al., 1985).

Cakir-Kiefer et al（2011）have discussed in vitro digestibility of α-casozepine, a benzodiazepine-like peptide from bovine casein, and biological activity of its main proteolytic fragment.

Zou et al. (2015) have indicated that bioactive peptides obtainedfrom porcine cerebral hydrolysate havetheability to protect from any effects by reducing the Pb_2C concentration of the blood and brain. Su et al. (2016) have revealedthat Coiliamystusproteinhydrolysate has therapeutic potential for memory deficit through inhibition of acetyl-cholinesterase (AChE).

Table 3.Effects of bioactive peptides on nervous system.

Bioactive Peptides onGastrointestinal System

Effects	Origin	Amino acid sequence (in single-letter code)	Reference
Opioid and antinociceptive peptides	Wheat	GYYPT, YPISL	Takahashi et al., 2000; Fukudome and Yoshikawa, 1993
	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 peptides	Bovine Casein	YLGYLEQLLR, YLGYLEQ	Cakir-Kiefer et al., 2011; Messaoudi et al., 2005
	Bovine as1-casein	YLGYLEQLLR	Miclo et al., 2001; Hernandez-Ledesma et al., 2014
	Bovine milk lactoferrin	—	Takeuchi et al., 2003; Kanemori et al., 2004

Bioactive Peptides onGastrointestinal System

Table 3 presents an overview of reported effects of peptides on gastrointestinal system.Micewicz et al., 2015 has mentioned that 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.

Beucher et al. (1994) has showed that glycomacropeptide is released fromdietary casein during gastric digestion via stimulation of CCK release by intestinal cells. It also is supported by Pedersen et al. (2000), whoindicatedthat dietary amount of CMP can stimulate pancreatic secretion through CCK release. In vivostudy, There are many recent researches for bioactive peptides and proteins have been considered for their effects on probiotics (Oda et al.,2013, Nishi et al., 2003a, Yu et al.2016).

Table 3. Effects of bioactive peptides on gastrointestinal system.

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

Mineral binding

Caseinophospopeptides simulate mineral binding properties and are useful in dental care. They also increase the absorption and bioavailability of calcium and some other minerals, such as manganese, zinc, copper and iron in the intestine. Most Caseinophospopeptides have a common design, such as a sequence of three phosphoseryl followed by two glutamic acid residues (Gobbetti et al. 2007).

These sequences provide the peptides with the unique capacity to keepCa, P and other mineral in a solution at intestinal Ph. Most phospopeptides containing the cluster sequence -Ser(P)-Ser(P)-Ser(P)-Glu(E)-Glu(E)- have been identified from whole bovine casein (Sharma et al. 2011).The negatively charged side chains, represent the binding sites for minerals (Gobbetti et al. 2007).

Table 4. Commerciallyproducts of peptides.

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	Porphyrayezoens is	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

Food Protein-Derived Bioactive Peptides

The primary purpose of protein consumption is to provide essential amino acids, which are used by the body to synthesize various structural (muscles, bones, hair) and functional (enzymes, hormones) proteins required for homeostasis maintenance. However, the increasing popularity of functional foods and nutraceuticals has led scientists to seek protein-derived fragments (peptides) that could prevent or even treat chronic metabolic disorders. A bioactive peptide consists of a certain number of amino acids (2-20) that are usually encrypted (hence the term 'cryptides') within the linear protein chain (Figure. 2) and remain inactive until released by digestion.

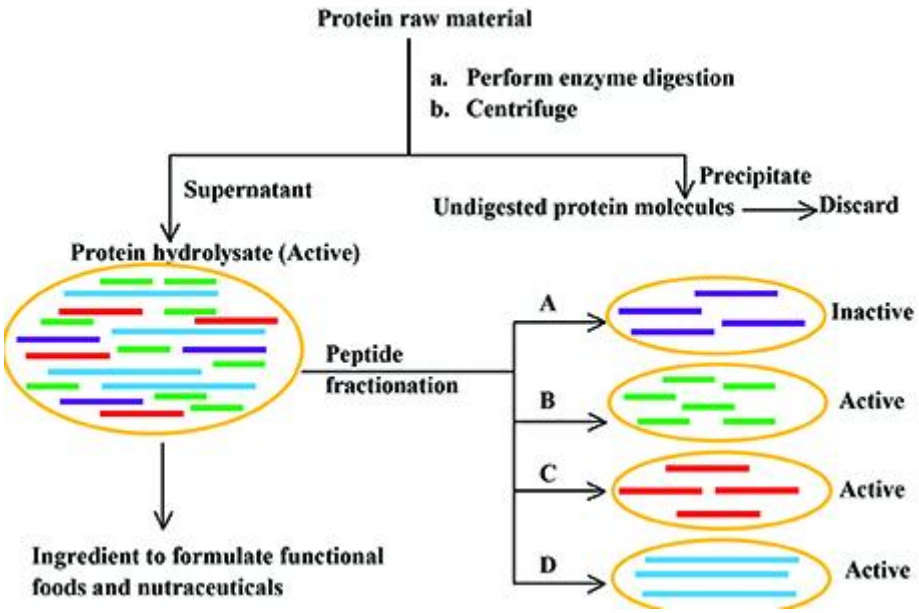

Figure. 2 Food Protein-derived Bioactive Peptides.

A protein chain can contain several cryptides that may be similar (same length and amino acid sequence) or dissimilar (same or different length with different amino acid sequence). Thus, it follows that under appropriate gastrointestinal tract (GIT) digestion conditions, food proteins could yield bioactive peptides. High peptide solubility increases absorption potential during oral consumption and hence ensures a more effective

bioavailability. This method produces a 'peptide soup' called a protein hydrolysate that contains cryptides and non-cryptides with peptides of different sizes, amino acid composition or sequence and activity. The protein hydrolysate can be tested for desirable activity and if positive may be used directly to formulate functional foods and nutraceuticals. High levels of cryptides will enhance bioactive properties of the protein hydrolysate. Therefore, subsequent separation techniques (membrane ultrafiltration, column chromatography) can be used to enrich the product with highly active peptides (fractions B, C, D) through removal of the inactive or less active components (fraction A) as shown in Fig. 1. Peptide separation is based mainly on size, net charge and hydrophobicity to produce distinct and homogenous fractions with better bioactive properties than the original protein hydrolysate. However, in some cases, peptide separation actually produces fractions with reduced bioactive properties than the original protein hydrolysate. The strong bioactive properties of such protein hydrolysates has been attributed to synergistic effects whereby the peptide interactions produce stronger effects than the sum of individual peptides. Therefore, loss of synergy as a result of peptide separation causes reductions in bioactive effects of the peptide fractions; in such cases, use of the protein hydrolysate without further peptide separation is preferred

Challenges In Bioactive Peptides Application

Challenges in application of bioactive peptides and hydrolysates in industries have been discussed by many authors (Lafarga and Hayes2016, Harnedy and FitzGerald, 2012; Lafarga and Hayes, 2016;Korhonen2009).

Grienke et al. (2014) has pointed to the importance of collaboration to reach a condition to exploit favorable bioactive peptides foods.

Another application of bioactive peptides and hydrolysatesis related to the effects of peptides on humans. Although there have been several in vivo investigations proving the bioactivity of peptides and hydrolysates inanimal models, the results of these studies cannot be confidently generalized to humans.

Different methods have been proposed to reduce bitterness of the peptides. The degree of bitterness isevaluatedin mole concentration of quinine sulfate solution (Matsuoka et al., 1991; Habibi-Najafiand Lee, 1996).

Peptides that reduce cell proliferation may be important tools in the fight against cancer. Using various cancer cell lines (liver, breast and cervical), rapeseed peptides obtained through fermentation significantly reduced cell proliferation but without cell toxicity. Similarly, a peptide (Trp-Pro-Pro) isolated from an enzymatic hydrolysate of blood clam muscle showed toxicity and antiproliferative effects when incubated with various cancer cell lines. In the presence of Trp-Pro-Pro (5 and 15 mg/ml), apoptosis of human prostate cancer cells (PC-3) increased 2-fold, which suggests anticancer potentials for the peptide. Cowpea protein hydrolysates have demonstrated potential cholesterol-reducing abilities through in vitro inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the enzyme that catalyzes the rate determining step during hepatic cholesterol synthesis37. If absorbed from the GIT, the cowpea protein hydrolysate could interfere with and decrease in situ cholesterol synthesis, which would lead to lowering of blood cholesterol and associated health benefits. The cowpea protein hydrolysate also interfered with micellar solubilization of cholesterol during in vitro tests. Since cholesterol solubilization is an important prerequisite for absorption from the GIT into blood circulation, consumption of the micellar-disrupting cowpea protein hydrolysate may enhance fecal removal of cholesterol and promote low blood cholesterol levels. Protein hydrolysates have also been tested for immune-modulating activities, especially to promote cellular expression of anti-inflammatory hormones (cytokines). Using a lipopolysaccharide/interferon γ-stimulated RAW 264.7 NO(-) macrophages, PPH treatment was shown to inhibit NO production by up to 20% when compared to non-treated cells38. The PPH also significantly inhibited secretion of the pro-inflammatory cytokines, TNF-α and IL-6, by 35 and 80%, respectively. Mice that received an oral administration of PPH displayed enhanced peritoneal macrophages phagocytic activity in addition to stimulated gut mucosa immune response. The enhanced immune response was typified by an increased number of IgA+ cells in the small intestine lamina propria as well as higher numbers of IL-4+, IL-10+ and IFN-γ+ cells38. The authors concluded that the PPH may be used as an alternative therapy to prevent inflammatory-related diseases.

To sum up, there is still a long investigationto make use of bioactive peptides from natural resources. In recent years, many companies have beeninclined toward manufacture of foods from bioactive peptides. This may be caused by two main factors, technical and price. Functional foods have accounted for the major part of products depend on bioactive peptides and hydrolysates from the nature. Moreover, medicalapplications of this kind ofpeptides areforbiddenbecause of their toxicity of the peptides when applied systemically. Fully synthetic peptides and peptidomimeticshave been proposed to overcome any problems. Production of anti-aging cosmetics isbased on bioactive peptides from natural resources with appropriate level.

II. CONCLUSION

There are many varietiesof resources of protein hydrolysatesfrom plant, animal origins, chemical, enzymatic, and microbial procedures. Different effects on immune, cardiovascular, nervous, and gastrointestinal systems have been discussed. They have also discussed the functional and antioxidant properties in food systems. Applications of bioactive and challengesdepend on the sources from which the peptides and hydrolysates are

obtained. Different methods have been discussedto 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.

Recentlya trend in this regard for the characterization and purification of peptides with stronger and more specific effects has beenshown.Although,the recent research is focused in the production of peptide-based foods, there is still a big gap between wide academic findings and commercialization of bioactive peptides from natural products.By considering bioactive activities of these peptides and their effect on health, and millions of deaths caused diseases, it is clear that these peptides can be used for health promotion and slowing down disease risk.

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Dauda Sa-Adu Abiola" Bioactive peptides from meat and some daily food and their role on human health and nutrition" International Journal of Engineering And Science, vol. 09, no. 01, 2019, pp. 40-51