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Health Promoting Effects of Food-Derived Bioactive Peptides: A Review

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Abstract
Bioactive peptides are functional agents encrypted in food proteins with several potential health benefits. Food-derived proteins when hydrolysed release large variety of bioactive peptides which are similar in structure to peptide sequences acting in the organism as endogenous signals, or hormones and alter their physiological functions. Moreover, these bioactive peptides owing to their high tissue affinity, specificity and efficiency can interact with receptors, enzymes and certain biomolecules in organism thereby confer health promoting effects. In addition, several studies have revealed that these peptides exhibit beneficial effects for the treatment and management of chronic and several degenerative diseases including hypertension, diabetes, obesity and cancer. Therefore, this review mainly used ISI, SCOPUS and PubMed indexed journals containing various experimental reports on in vitro and in vivo studies from humans and animals to elucidate the potential health promoting effects of food-derived bioactive peptides with emphasis on antihypertensive peptides, antidiabetic peptides, cholesterol-lowering peptides, anticancer peptides, and antimicrobial peptides.

Keywords Degenerative diseases · Food · Bioactive peptides · Health benefits · Mechanism of action

Introduction

There is increase in epidemiological evidences linking the prevalence of lifestyle-related diseases including hypertension, obesity, diabetes, and cancer to dietary factors (Hernández-Ledesma et al. 2011; Gul et al. 2015; Daliri et al. 2017). Consequently, functional foods are emerging in response to the increased perception about the relation of food and health benefits. The protein in foods serves both nutritional and physiological roles (Daliri et al. 2017). Food protein can be hydrolysed to produce several bioactive peptides with different potential health benefits. Bioactive peptides are active fragments, but they remain inactive as long as they remain locked in the parent protein (Hernández-Ledesma et al. 2014). These bioactive peptides are produced by enzymatic hydrolysis of the parent proteins as well as during food processing such as cooking, fermentation and ripening (Palaniswamy et al. 2012; Yahya et al. 2017; Daliri et al. 2017). Bioactive peptides are known to specifically interact with biomolecules and certain receptors thereby modulate their physiological functions (Daliri et al. 2017; Hayes 2018). The production of bioactive peptides and their possible incorporation into food is gaining interest particularly owing to their health promoting effects and safety (Reddi et al. 2016; Daliri et al. 2017; Lin et al. 2018). The classical approach involves enzymatic proteolysis with food-grade proteolytic enzymes to release numerous peptide fragments in hydrolysate (Ugwu et al. 2019; Abdel-Hamid et al. 2017; Babini et al. 2017; Wang et al. 2017). Also, bioactive peptides can be produced from parent proteins by the use of proteolytic system of microorganism during fermentation (Hernández-Ledesma et al. 2014; Koyama et al. 2014; García-Tejedor et al. 2015; Aguilar-Toalá et al. 2017). The biologically active peptides generated can be subjected to purification, sequence synthesis and then formulated as functional foods or nutraceuticals (Daliri et al. 2017). Moreover, in silico proteolysis has been employed by several researchers to identify potential bioactive peptide sequences and also elucidate their mechanism of actions via molecular

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docking analysis (Schneidman-Duhovny et al. 2005; Masuyer et al. 2012; Lin et al. 2018; Ugwu et al. 2019). Therefore, this review mainly used ISI, SCOPUS and PubMed indexed journals containing various experimental reports on in vitro and in vivo studies on humans and animals to elucidate the potential health promoting effects of foods-derived bioactive peptides with emphasis on antihypertensive peptides, antidiabetic peptides, cholesterol-lowering peptides, anticancer peptides, and antimicrobial peptides.

Production of Bioactive Peptides

Food-derived bioactive peptides are usually produced through enzymatic hydrolysis of their parent protein by enzymatic proteolysis (Mirzaei et al. 2018; Kumar et al. 2016), gastrointestinal digestion (Mohanty et al. 2016), microbial fermentation (Yahya et al. 2017) and in silico proteolysis (Ugwu et al. 2019; Lin et al. 2018). Besides, if the peptide sequence is known, it is also possible to synthesize the peptide via chemical or enzymatic synthesis or by genetic recombination using bacteria (Park et al. 1998; Lv et al. 2003; Jeong et al. 2007; Hernández-Ledesma et al. 2011).

Enzymatic Hydrolysis

In enzymatic hydrolysis, biologically active peptides can be produced through hydrolysis of the whole protein molecule using analytical-grade proteinases such as alcalase, chymotrypsin, pepsin, trypsin, elastase, flavourzyme, savinase, thermolysin, and pancreatin individually or combined (Mohanty et al. 2016; Kumar et al. 2016; Bamdad et al. 2017; Chaudhari et al. 2017; Ugwu et al. 2019). The process involves reconstitution of protein sample in appropriate buffer of different pH (the optimum pH of the hydrolytic enzymes) for optimum enzymatic action. The reconstituted protein solution has to be heated in water bath (95 °C) for 5 min to kill microorganisms, which may produce proteolytic enzymes during hydrolysis and also to denature the indigenous enzymes of proteins, if present. The optimum pH and temperature for the hydrolysis has to be standardized (Kumar et al. 2016). The enzyme/substrate ratio (E:S) should be kept at 1:100 (Kumar et al. 2016), 1:10 (Mirzaei et al. 2018), 3:1 (Lin et al. 2017) and 1:50 (Bamdad et al. 2017) for 4 h, 5 h, 4 h and 1 h respectively. Each hydrolyzed sample is immediately heated to 85 °C for 15 min in water bath to inactivate the residual enzyme left in hydrolysates (Kumar et al. 2016). The hydrolysate is allowed to cool, centrifuged in refrigerated centrifuge and then the supernatant obtained is subjected to further purification techniques (Bamdad et al. 2017) (Table 1).

Gastrointestinal Digestion

Biologically active peptides can also be released from food-derived proteins during gastrointestinal digestion by the action of digestive enzymes such as pepsin, trypsin, chymotrypsin and peptidases (Hernandez-Ledesma et al. 2011; Mohanty et al. 2016). Proteins from food sources are usually denatured in the presence of hydrochloric acid (HCl) secreted by the parietal cells of the stomach. This low pH mediates the activation of pepsinogen and its subsequent conversion to its active form called pepsin (Mohanty et al. 2016). These enzymes occur at the surface of epithelial cells where they release several peptides of different lengths. Some of these peptides exert direct function at the gastrointestinal tract while other peptides are absorbed via systemic circulation to reach target organs and tissues (Shimizu, 2004). Scientists have employed simulated digestion using different proteins such as milk proteins (Hernandez-Ledesma et al. 2004, 2007; Gomez-Ruiz et al. 2004; Lignitto et al.

Table 1 Enzymes applied in production of bioactive peptides by enzyme hydrolysis

Enzyme	Source	Activity[a]	Optimum conditions	Time (h)[b]	References
Alcalase	*Bacillus licheniformis*	≥ 2.4 U/g	pH 7.5; 25 °C	4	Kumar et al. (2016)
Chymotrypsin	Bovine pancreas	≥ 40 U/mg	pH 7.8; 37 °C	4	Kumar et al. (2016)
Pepsin	Porcine gastric mucosa	2500 U/mg	pH 2.0; 37 °C	4	Chaudhari et al. (2017)
Trypsin	Porcine pancreas	30 U/g	pH 7.0; 37 °C	4	Mirzaei et al. (2018)
Elatase	Hog pancreas	≥ 4 U/mg	pH 8.0; 37 °C	1	Bamdad et al. (2017)
Flavourzyme	*Aspergillus oryzae*	≥ 500 U/g	pH 7.0; 50 °C	1	Bamdad et al. (2017)
Savinase	*Bacillus sp.*	≥ 16 U/g	pH 7.0; 55 °C	1	Bamdad et al. (2017)
Thermolysis	*Bacillus thermoproteolyticus*	14 U/g	pH 7.0; 50 °C	1	Bamdad et al. (2017)
Pancreatin	Porcine pancreas	≥ 100 U/mg	pH 7.5; 40 °C	4	Chaudhari et al. (2017)
Papain	Papaya plant leaf	≥ 10 U/mg	pH 7.0; 65 °C	4	Kumar et al. (2016)

[a]Amount of substrate in moles converted to product per unit time

[b]Duration of hydrolysis

2010; Egger et al. 2017; Sanchón et al. 2018; Basilicata et al. 2018), soybean seeds (Capriotti et al. 2015; González-Montoya et al. 2018), soy milk proteins (Capriotti et al. 2015), egg proteins (Wang et al. 2018), meat protein (Anna et al. 2016; Wang et al. 2018), fish proteins (Borawska et al. 2016; Mora et al. 2017; Polona et al. 2017; Korczek et al. 2018; Zhang et al. 2018), plant protein (Pachaiappan et al. 2018) in order to examine how these gastrointestinal proteases mediate the proteolytic digestion of food proteins and release bioactive peptides which in addition to nutritional benefits may exert many physiological and health beneficial functions.

Fermentation

An alternative strategy for production of biologically active peptides uses the proteolytic system of microorganism (Hernández-Ledesma et al. 2014). For instance, during fermentation process, microorganisms hydrolyse proteins into peptides and amino acids which serve as nitrogen source necessary for their growth (Juillard et al. 1998). These bioactive peptides also can be isolated by centrifugation (Palaniswamy et al. 2012) and purified through ultrafiltration or molecular sieve (Mirzaei et al. 2018), and the amino acid sequences of bioactive peptide are identified by chromatographic methods (Lin et al. 2017; Mirzaei et al. 2018). For example, IPP and VPPP are antihypertensive peptides produced by fermented milk protein using *Lactobacillus helveticus* and *Saccharomyces cerevisiae* (Nakamura et al. 1995). Also, fermentation of milk with *Enterococcus faecalis*, produced bioactive peptides (LHLPLP and HLPLP) which have demonstrated antihypertensive effect in rat model (Quirós et al. 2007).

The results of animal experiment and human trials suggest that fermented milk products may exhibit antioxidant effect associated with cardiovascular benefits (Hernández-Ledesma et al. 2014). Furthermore, the consumption of fermented goat milk by healthy individuals improved the total plasma antioxidant activity (Hernández-Ledesma et al. 2014). Although the compounds responsible for these effects have not yet been identified, however the peptides released in fermentated milk might have a key role (Hernández-Ledesma et al. 2014).

According to Yahya et al. bioactive peptides in milk are released by fermentation of skim milk using *L.helveticus* and *S. thermophilus* and these peptides have shown antihypertensive effects on spontaneously hypertensive rats (Yahya et al. (2017). Furthermore, Palaniswamy et al. used the proteolytic system of *Lactobacillus plantarum* isolated from commercially available dairy products to generate milk hydrolysates from goat milk. The hydrolysates obtained exhibited ACE-inhibitory and antioxidant properties (Palaniswamy et al. 2012). Although, the amino acid sequences of the bioactive peptides present in the hydrolysates responsible for ACE-inhibitory and antioxidant activity were not identified yet, but the bioactive peptide released in the fermentation product could be responsible.

Genetic Engineering

Recombinant DNA technology is being exploited for mass production of biologically active peptides (Schrimpf et al. 2018; De Brito et al. 2018) especially for the synthesis of long chain peptides and proteins (Chahardoli et al. 2018; Boga et al. 2018). This method involves the construction of peptides coding region and its subsequent cloning into a prokaryotic expression vector using *E. coli* cells as host. This allows the production of several peptides, simultaneously (Espita et al. 2009). However, one of the challenges of this technique is that the expression products may be harmful to the host (Hernández-Ledesma et al. 2011). Moreover, antibacterial peptides possess strong antibacterial activity against the expression vector cells and relative sensitivity to proteolytic enzymes (Espita et al. 2009). Interestingly, these shortcomings have been overcomed by expression of these peptides in the forms of a fusion protein or a tandem gene to neutralize their inherent toxic properties and improve their expression levels (Espita et al. 2009; Hernández-Ledesma et al. 2011). For example, ACE-inhibitory peptides with amino acid sequences HHL, HVLPVP, FFVAPFPEVFGK, and GHIATFQER have been expressed successfully in *E. coli* (Park et al. 1998; Lv et al. 2003; Jeong et al. 2007; Liu et al. 2007). Although promising results are being obtained, notwithstanding, the use of genetically modified microorganisms in food products is still controversial.

Purification and Characterization of Bioactive Peptides

The techniques mostly employed in production of bioactive peptides usually generate crude peptides which required further purification processes. This is because crude peptide consists of a mixture of peptides, residues of reagents and products of side reactions (Espitia et al. 2012). Thus, different separation techniques are used for purification of these crude peptides. In the initial stage of the purification process, the crude hydrolysates are subjected to centrifugation (Palaniswamy et al. 2012) followed by ultrafiltration using molecular weight cut off membranes (Bamdad et al. 2017; Chaudhari et al. 2017). Subsequently, the partially purified peptides are put through any of the reversed-phase high-performance liquid chromatography (RP-HPLC), ion-exchange chromatography, size exclusion chromatography, affinity chromatography, or capillary electrophoresis (Table 2).

The purity of a peptide is usually verified by a method different from the one used for purification process. Thus, the characterization is carried out by different methods of

Table 2 Different purification methods of bioactive peptides

Method	Fundamental principle	References
Reversed-phase chromatography	Hydrophobicity; stationary phase of lower polarity and mobile phase of higher polarity	Mirzaei et al. (2018)
Size exclusion liquid chromatography	Based on size of the peptide relative to pore size of stationary phase	Bamdad et al. (2017)
Capillary electrophoresis	Migration of peptides in an electric field based on its charge in solution	Chetwynd et al. (2018)
Ion exchange chromatography	Interaction of charged groups of the peptides with the surface of stationary phase	Yigzaw et al. (2009)
Affinity chromatography	Based on the biological specificity and interaction of the peptide and the ligand immobilized in the column	Pina et al. (2014)

mass spectrometry such as electrospray ionization mass spectrometry (ESI–MS), fast atom bombardment mass spectrometry (FAB-MS) or matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) (Espitia et al. 2012; Bamdad et al. 2017) (Fig. 1).

Health Beneficial Effects of Bioactive Peptides

Bioactive peptides are 2 to 20 amino acid residues present in the parent proteins, they act as endogenous signals, or hormones in the organism (Hernández-Ledesma et al. 2014)

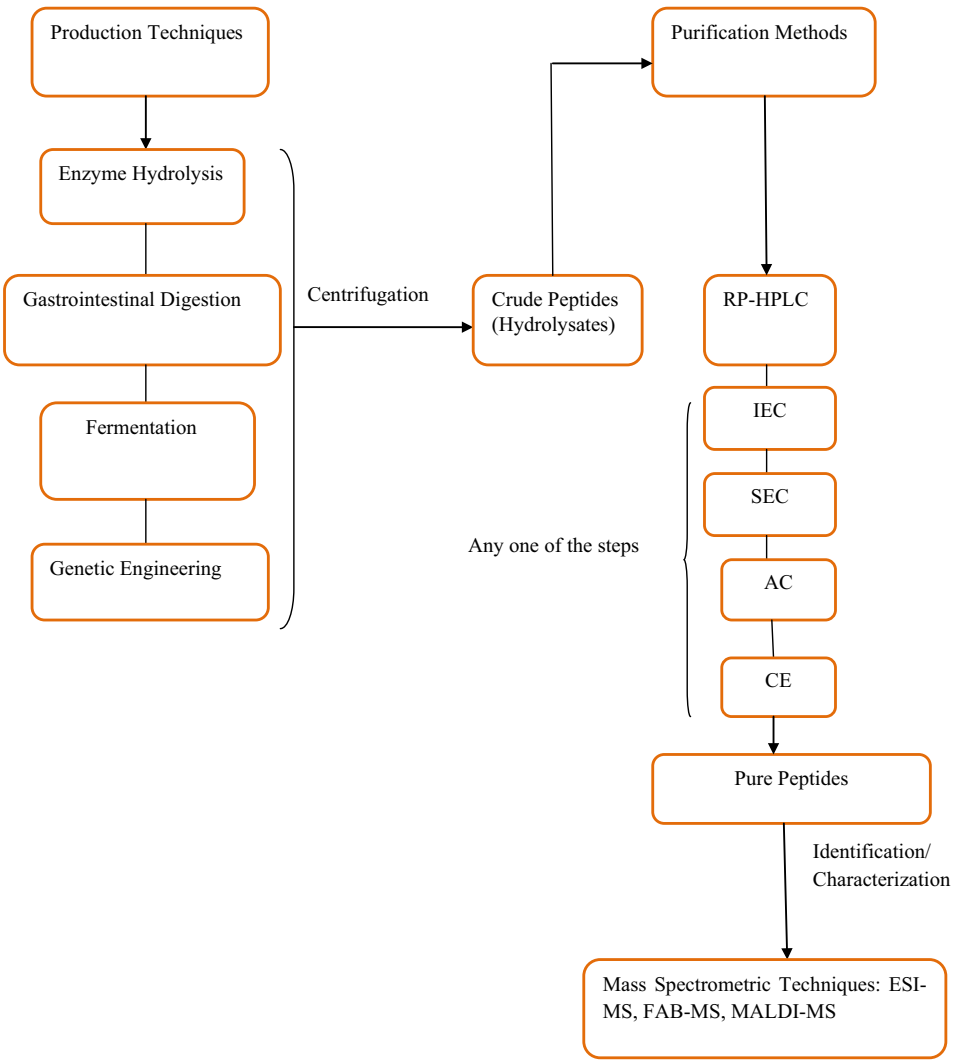

Fig. 1 Production, purification and characterization of bioactive peptides: *RP-HPLC* reversed phase- high performance liquid chromatography, *IEC* ion exchange chromatography, *SEC* size exclusion chromatography, *AC* affinity chromatography, *CE* capillary electrophoresis, *ESI–MS* electrospray ionization mass spectrometry, *FAB-MS* fast atom bombardment mass spectrometry, *MALDI-MS* matrix-assisted laser desorption/ionization mass spectrometry

by interacting with certain receptors and biomolecules to modulates their biological functions (Hernández-Ledesma et al. 2014). The inherent characteristic of the amino acid residues present in the peptide sequences are mainly responsible for the biological activities including ACE-inhibitory, antidiabetic, cholesterol lowering, antibacterial, Immunomodulatory, and antioxidative effects (Pihlanto 2006; Zou et al. 2016; Daliri et al. 2017; Khan et al. 2018). Therefore, bioactive peptides when exploited could be beneficial for treatment and management of numerous life style-related diseases.

Antihypertensive Peptides

ACE-Inhibitory Peptides

Hypertension is one of the major risk factors for cardiovascular disease (Erdmann et al. 2008). Angiotensin converting enzyme (EC 3.4.15.1) is one of the main regulators of blood pressure and it is a key component of the renin–angiotensin–aldosterone system (RAAS). The RAAS pathway starts with renin converting angiotensinogen into angiotensin I. Angiotensin I is then converted to angiotensin II via angiotensin converting enzyme (ACE) activity. Angiotensin II mediates vasoconstriction and activates aldosterone release from adrenal gland (Nawaz et al. 2017). Aldosterone is a steroid hormone that increases the expression of epithelial sodium channels which leads to sodium and water reabsorption resulting in hypertension (Nawaz et al. 2017). Yet in another mechanism, the kinin–kallikrein system (KKS), indicated that ACE cleaves the terminal dipeptide (Phe–Arg) of the vasodilator, bradykinin to its inactive form bradykinin 1–7 (Imig 2004). Thus, inhibition of this enzyme is considered as one of the strategies for treatment of hypertension. Owing to the facts that many synthetic antihypertensive drugs have been reported to exhibit adverse effects such as dizziness, dysgeusia, headache, angioedema, and cough (Daliri et al. 2016), there is a rapid growing demand for food-derived bioactive peptides with health-promoting effect and safety (Daliri et al. 2017). In recent years, anti-hypertensive effects of food-derived bioactive peptides in vitro and in vivo have been reported (Hernandez-Ledesma et al. 2014; Capriotti et al. 2015; Korczek et al. 2018). In addition, antihypertensive peptides possess remarkable high tissue affinities and thus eliminated slowly from tissues compared to synthetic drugs (Koyama et al. 2014). Some of the antihypertensive peptides are presented in Table 3.

Cholesterol-Lowering Peptides

Cholesterol is required by the body for synthesis of vitamin D, steroid hormones, and bile acids. However, hypercholesterolemia leads to formation of plaques in arteries resulting in arteriosclerosis and subsequent hypertension (Daliri et al. 2017). Also, cholesterol plaques in the coronary artery may reduce oxygen supply to the heart leading to cardiovascular diseases. Synthetic drugs employed for treatment of hypercholesterolemia cause liver injury, myopathy and diabetes (Katsiki and Banach 2012; Carter et al. 2013; Mancini et al. 2016). Thus, search for bioactive peptides with cholesterol lowering ability has increased over the years and many have been discovered with potential hypercholesterolemic effect (Table 4).

Antioxidant Peptides

High blood pressure is characterized by increase in reactive oxygen species (ROS) production and dysfunctional endogenous antioxidant mechanisms (Lassegue and Griendling 2004). The inability of the antioxidant mechanisms of the body to scavenge free radicals produced due to pathophysiological conditions results in induction of oxidative stress which in turn leads to tissue injury (Panth et al. 2016). Some of the risk factors for cardiovascular diseases (CVDs) such as diabetes mellitus, aging, smoking, hypercholesterolemia, and nitrate intolerance can increase the production of ROS (Panth et al. 2016). In addition, these risk factors can also trigger apoptosis, activation of metalloproteinases, proliferation and migration of smooth muscle cells, lipid peroxidation and change in vasomotor functions, all resulting to CVDs (Panth et al. 2016). Reactive Oxygen Species with unpaired electrons, such as superoxide anion ($O2^{\cdot-}$), hydroxyl radical ($OH^{\cdot-}$) and lipid radicals, are referred to as free radicals. Others such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl), have oxidizing effects capable of causing oxidative stress (Mada et al. 2017). For instance, the reactions of free radicals with fatty acids such as polyunsaturated fatty acids (PUFAs) within the cytoplasmic membrane generate fatty acid peroxyl radical which can attack the adjacent side chain of the fatty acid and trigger the production of other lipid radicals. The lipid radicals generated target the plasma membrane and may have adverse effect on cell function, including alteration in cell membrane permeability and dysfunction of membrane bound receptors (Bayir 2005; Mada et al. 2018). Free radicals are implicated in hypertension because they oxidize low density lipoproteins (LDLs) thereby promoting atherosclerosis (Paudel et al. 2016). Oxidized-LDLs is available in the arterial wall and macrophages take up oxidized-LDLs through scavenger receptor pathways resulting in cholesterol ester-rich foam cells and endothelial cell dysfunction, in part, via the role of lectin-like oxidized-LDLs receptor-1 (Mitra et al. 2011; Paudel et al. 2016). The foam cells secret calcium-dependent zinc containing endopeptidase and matrix metalloproteinase which are activated during oxidative stress in part because of inflammation and non-laminar

Table 3 ACE-inhibitory peptides

Peptide sequence	Origin	Method of production	References
LPESVHLNK	Kluyveromyces marxianus protein	Enzyme hydrolysis using trypsin and chymotrypsin	Mirzaei et al. (2018)
YVVFK	Soybean seeds and soy milk protein	Simulated gastrointestinal digestion using pepsin and pancreatin	Capriotti et al. (2015)
APGAPGPVG, HYVPV	Chicken hydrolysates (collagen)	Simulated gastrointestinal digestion using pepsin, trypsin and chymotrypsin	Anna et al. (2016)
RNLQGENEEEDSGA	Germinated soybean protein	Simulated gastrointestinal digestion using pepsin and pancreatin	González-Montoya et al. (2018)
AHLL	Apalbumin 2	Simulated gastrointestinal digestion using pepsin, trypsin and chymotrypsin	Xu and Gao (2015)
AAATP	Porcine skeletal muscle protein	Fermentation by meat-borne lactobacillus	Castellano et al. (2013)
PFPGPIPN	Qula β-casein-f 76–83	Enzyme hydrolysis using proteinases k from *Tritirachium album*	Lin et al. (2017)
LHLPLP	Qula β-casein-f 148–153	Enzyme hydrolysis using proteinases k from *Tritirachium album*	Lin et al. (2017)
QKEPMIGV	Qula β-casein-f 146–153	Enzyme hydrolysis using thermolysin (from *Tritirachium album*)	Lin et al. (2017)
KYIPIQ	Qula k-casein-f 45–50	Alcalase (from *Bacillus licheniformis*) hydrolysis	Lin et al. (2017)
LPLPLL	Qula β-casein-f 150–155	Trypsin (from porcine pancreas) hydrolysis	Lin et al. (2017)
VVSLSIPR	Pigeon pea seeds	Fermentation using *Aspergillus niger*	Nawaz et al. (2017)
SLPQNIPPL	β-casein-f 69–77	Fermentation using *Lactococcus lactis*	Rodriguez-Figueroa et al. (2012)
FFVAPFPEVFGK	Milk protein	Recombinant DNA technology using *Escherichia coli*	Lv et al. (2003)
HVLPVP	Milk protein	Recombinant DNA technology using *Escherichia coli*	Liu et al. (2007)
DVWY, FQ, VVG, VAE, WTFR	Buckwheat sprout	Neo-fermentation	Koyama et al. (2014)
DPYKLRP, PYKLRP, YKLRP, GILRP	Lactoferrin	Fermentation using *Kluyveromyces marxianus*	García-Tejedor et al. (2015)
AQSAP,IPAVF, APLRV, AHKAL	Whey from bovine milk	Fermentation using *Lactobacillus helveticus*	Daliri et al. (2017)
SY	Jelly fish gonads	Enzyme hydrolysis using neutrase	Zhang et al. (2018)

G glycine, *A* alanine, *P* proline, *V* valine, *L* leucine, *I* isoleucine, *M* methionine, *F* phenylalanine, *Y* tyrosine, *K* lysine, *R* arginine, *H* histidine, *S* serine, *T* threonine, *C* cysteine, *N* asparagine, *Q* glutamine, *D* aspartate, *E* glutamate

Table 4 Cholesterol-lowering peptides

Peptide sequence	Origin	Method of production	References
IIAEK	β-Lactoglobulin	Trypsin hydrolysis	Nagaoka et al. (2001)
HIRL	β-Lactoglobulin	Chymotrypsin hydrolysis	Yamauchi et al. (2003)
LPYP, IAVPGEVA, IAVPTGVA	Soybean protein	Soy glycinin digestion with trypsin	Lammi et al. (2015)
HSDADYVLVVLNGR, HGREEEEEEEEEDER, YPSSTKDQQSY	White lupin seed	Enzyme hydrolysis using pepsin and trypsin	Lammi et al. (2016)
YAAAT	Black bean and cowpea	Pepsin-pancreatin digestion	Hernandez and de Mejia (2017)

shear stress (Harrison, 1997).This is one of the important steps in the progression and development of atherosclerosis (Harrison et al. 2003). Atherosclerosis disrupts the flow of blood due to plaque buildup on the artery wall leading to more resistance in blood vessels thereby causes increase in blood pressure. Food-derived peptides exhibit antioxidant property without side effects (Shanmugam et al. 2015; Sarmadi and Ismail 2010). Consequently, many peptides with antioxidant properties have been discovered (Table 5).

Mechanism of Action of Angiotensin-Converting Enzyme (ACE) Inhibitory Peptides

ACE inhibitory peptides usually consist of short amino acid sequence (He et al. 2013) with tyrosine, phenylalanine, tryptophan, lysine, leucine, isoleucine, valine and arginine as dominant amino acids (Murray and Fitzgerald 2007). In addition, peptides containing hydrophobic amino acids are the most effective ACE inhibitors especially those with proline in the C-terminal and positively charged amino acids (arginine and lysine) in the N-terminal (Lemes et al. 2016). Likewise, presence of branched chain amino acids such as valine and isoleucine in the peptide sequence promotes hydrophobic interaction at the ACE active site ensuing inhibition the enzyme (Daliri et al. 2017). Similarly, casein-derived peptides contain phosphorylated serine residue which are effective cation chelators that form complexes with Zn^{2+} in the active site of ACE to prevent metal ion catalysis (Daliri et al. 2017). Also, bioactive peptides with histidine and glutamate residues acts as Zn^{2+} chelators thereby enhances ACE inhibition (Fitzgerald et al. 2004; Pihlanto 2006; Daliri et al. 2017).Consequently, the ratio of hydrophilic-hydrophobic amino acids in the peptide sequence is a critical factor in ACE-inhibitory activity due to disruption of access of the peptides to ACE active site by hydrophilic amino acid residues (Mirzaei et al. 2018; Asoodeh et al. 2016; Li et al. 2004). Researchers have revealed that ACE prefers substrates or competitive inhibitors that contain aromatic amino acid residues such as tryptophan, phenylalanine and tyrosine at their C-terminal tripeptide sequence as well as branched and aliphatic amino acids such as glycine, valine, leucine, and isoleucine at the N-terminal (Kapel et al. 2006; Ondetti and Cushman 1984; Sharma et al. 2011). Besides, molecular docking analysis have shown that ACE-inhibitory peptides combine with ACE residues through the interaction forces of hydrogen bonds, hydrophobic, van der waals and electrostatic interactions that exist between amino acids residues of ACE and those of peptides (Li et al. 2014). However, hydrogen bonds interaction force plays crucial role for stabilizing the docking complex and enzyme catalytic reactions (Mirzaei et al. 2018). Wu et al. reported that ACE contained three main active site pockets

Table 5 Antioxidative peptides

Peptide sequence	Origin	Method of production	References
LLSGTQNQPSFLSGF, NSLTLPILRYL,TLEPNSVF- LPV-LLH	Lentil protein	Enzyme hydrolysis using savinase	Garcia-Mora et al. (2017)
YSK	Rice bran protein	Trypsin hydrolysis	Wang et al. (2017)
WVYY, PSLPA	Hemp seed (*Cannabis sativa* L.)	Simulated gastrointestinal digestion using pepsin and pancreatin	Girgih et al. (2014)
YVEELKPTPEGDL	Buffalo ricotta cheese	Simulated gastrointestinal digestion using pepsin, pancreatin and chymotrypsin	Basilicata et al. (2018)
VLSTSFPPK	Kluyveromyces marxianus protein	Enzyme hydrolysis using trypsin and chymotrypsin	Mirzaei et al. (2018)
VLYSTPVKMWEPGR, VITV-VATAGSETMR, HIGININSR	*Tinospora cordifolia* stem proteins	Enzyme hydrolysis using trypsin, papain, pepsin, α-chymotrypsin, and pepsin-pancreatin	Pachaiappan et al. (2018)
WG	Poultry protein	Simulated gastrointestinal digestion using pepsin trypsin and chymotrypsin	Anna et al. (2016)
PGPIPN, PFPGPIPN, YPFPGPIP, VYPFPGPIPN, MPFPKYPVEP, EPVLGPVRGPFP, QEPVLG-PVRGPFP, TPVVVPPFLQPE, TQTPVVVPPFLQPE	Casein from bovine milk	Enzyme hydrolysis using flavourzyme, savinase, thermolysin, trypsin, and elastase.	Bamdad et al. (2017)
AEERYP, DEDTQAMP	Chicken egg white	Protease hydrolysis	Nimalaratne et al. (2015)
VLPVPQK	Buffalo milk casein	Trypsin-pepsin hydrolysis	Shanmugam et al. (2015), Mada et al. (2017)

viz: S1, S2, and S01 (Wu et al. 2015). The first pocket (S1) contained Ala354, Glu384 and Tyr523 residues, and S2 pocket consisted of Glu281, His353, Lys511, His513 and Tyr520 residues, while S01 included Glu162 residue. Also previous molecular docking study revealed that VLSTS-FPPK, LPGSVHLAK peptides formed hydrogen bond with the S1, S2 and S01 pockets and inhibited ACE activity (Mirzaei et al. 2018) (Fig. 2).

Mechanism of Action of Cholesterol-Lowering Peptides

Biologically active peptides that possess hypocholesterolaemic effect are also crucial in the management of hypertension. For example, Cumin seed derived peptides have been shown to inhibit cholesterol micelle formation, inhibit lipase activity and bind strongly to bile acids and may therefore lower cholesterol level (Siow et al. 2016). Previous study also revealed that sericin-derived oligopeptides suppressed serum total cholesterol and inhibited cholesterol uptake by monolayer cells. These peptides also bound tightly to taurocholate, deoxytaurocholate, and glycodeoxycholate which lead to a reduced cholesterol absorption in the gut (Lapphanichayakool et al. 2017). Additionally, Lammi et al. reported that soybean peptides (LPYP, IAVPGEVA and IAVPTGVA) activated LDLR-SREBP-2 signaling pathway, improved LDL absorption and inhibit HMG-CoA reductase activity in HepG2 cells and this may account for their significant hypocholesterolaemic effect (Lammi et al. 2015). In a related studies, peptides derived from cowpea and rice bran protein hydrolysates exhibited HMG-CoA reductase-inhibitory effect and reduced cholesterol micellar solubilization in vitro (Marques, et al. 2015; Zhang et al. 2012). Moreover, black bean and cowpea-derived peptide (YAAAT) can bind tightly to the N-terminal domain of Niemann-Pick C1 (NPC1L1) and disrupt the interactions between NPC1L1 and membrane proteins thereby improve cholesterol absorption (Hernandez and de Mejia 2017) (Fig. 3).

Mechanism of Action of Antioxidative Peptides

Antioxidative activity of bioactive peptides is associated with the composition, sequence and hydrophobicity of amino acid residues present in the peptide sequence (Lassoued et al. 2015). Also presence of hydrophobic amino acids in peptides sequence enhances their solubility in lipid and facilitates accessibility to free radical species, thereby promoting antioxidant activity (Chen et al. 1996; Suetsuna et al. 2000; Qian et al. 2008). Previous study demonstrated that there exists a strong correlation between the antioxidant properties of peptides with hydrophobic and aromatic amino acid residues (Cheison et al. 2007). For instance, the presence of valine and leucine at the N-terminal and proline in the sequence of peptide contribute to its antioxidant activity (Chen et al. 1995). Additionally, the aliphatic groups in valine and leucine have high affinity to hydrophobic poly unsaturated fatty acids (Qian et al. 2008). Also, lysine-containing peptides possess antioxidant property, especially due to their ability to reduce Fe^{3+} to Fe^{2+} and to chelate Fe^{2+} and Cu^{2+} ions (Carrasco-Castilla et al. 2012; Huang et al. 2010). Phenylalanine acts as proton donor to electron deficient radicals and efficiently scavenge them (Duan et al. 2014) while bioactive peptide with histidine residue in the sequence act as oxygen quencher and hydroxyl radical scavenger due to its imidazole ring which act as proton donor (Pihlanto 2006;

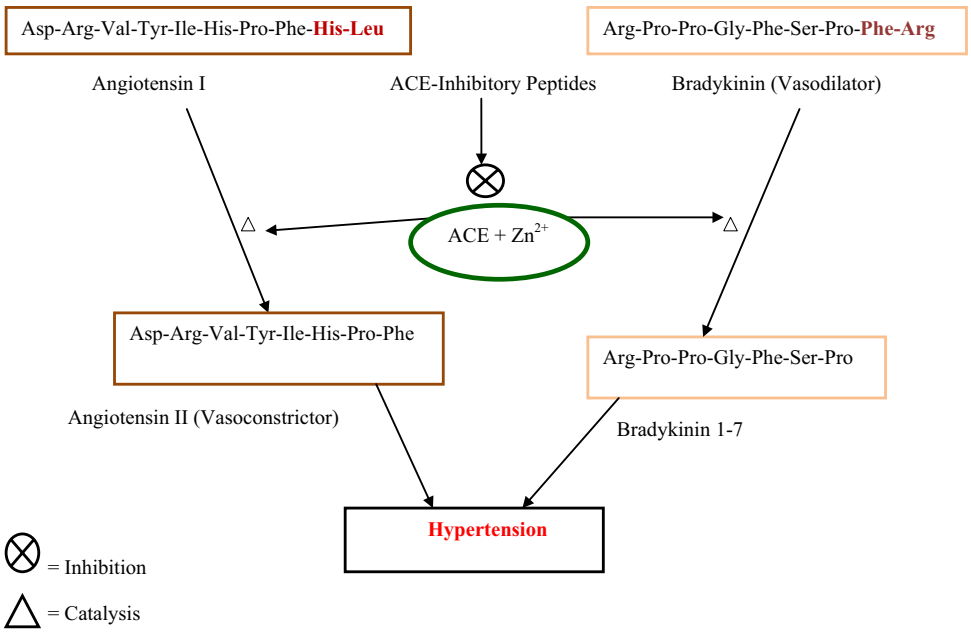

Fig. 2 ACE-catalyzed conversion of angiotensin I to angiotensin II and bradykinin to bradykinin (1–7). Formation of angiotensin II and depletion of bradykinin concentration results in elevation of blood pressure

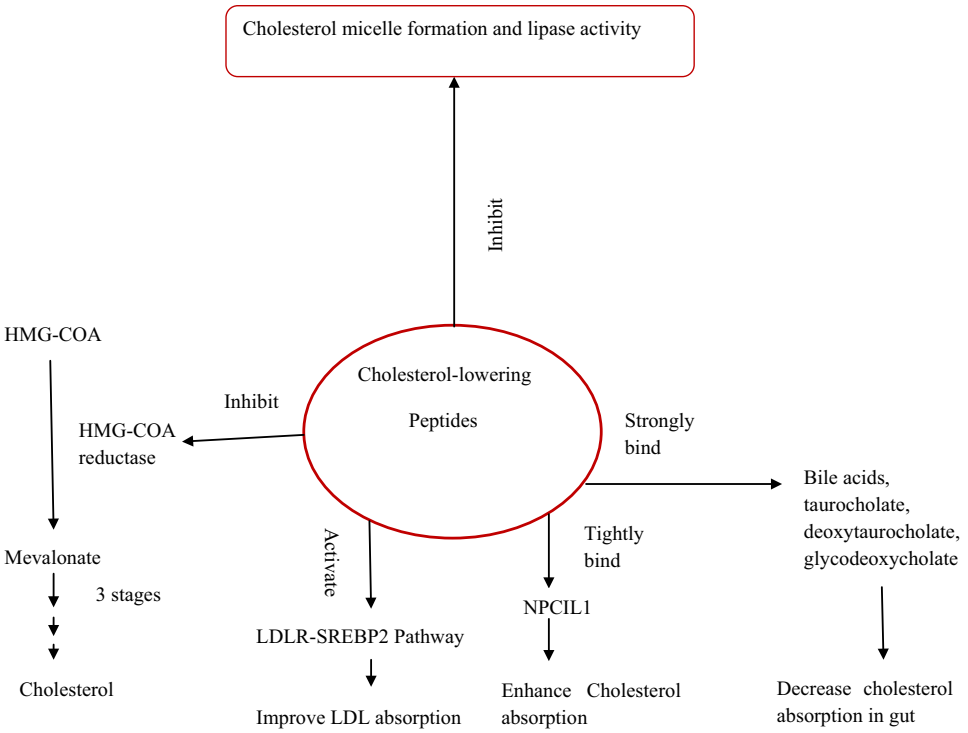

Fig. 3 Mechanism of action of cholesterol lowering peptides: *HMG-COA* 3-Hydroxy-3-methylglutaryl-coenzyme A, *LDLR-SREBP2* low density lipoprotein receptor-Sterol regulatory element binding protein 2, *NPCIL1* Niemann-Pick C1-like 1, *LDL* low density lipoprotein

Zou et al. 2016). In addition, tyrosine delivers a proton to suppress free radicals (Wang et al. 2008). Furthermore, the presence of histidine, proline, cysteine, tyrosine, tryptophan, phenylalanine, and methionine in a peptide sequence promotes delay in lipid peroxidation, thus producing antioxidant effect (Li and Yu 2015). Thus it is important to mention that antioxidative effect of a single amino acid is far weaker than the additive effect of many amino acids in the sequence of a bioactive peptide (Zhu et al. 2012) (Fig. 4).

Antidiabetic Peptides

Diabetes mellitus (DM) is a metabolic disease characterized by increased blood glucose level due to inadequate insulin secretion or action, or both. DM is classified as type I and type II. The Type I diabetes (Insulin dependent diabetes mellitus) is an autoimmune disease characterized by beta cells dysfunction leading to little or no insulin secretion by pancreas. Type 2 diabetes mellitus (T2DM) also known as non-insulin dependent diabetes mellitus, there is an imbalance in the insulin secretion and blood sugar absorption (Chaudhury et al. 2017). Unfortunately, the current therapy for diabetes uses synthetic drugs that have been linked with adverse effects and increases the risks of obesity (Thulé and Umpierrez 2014), gastrointestinal disorder (Thong et al. 2015), pancreatitis (Meier and Nauck 2014) and intolerance and other metabolic disorders (Dujic et al. 2015). However, bioactive peptides present in functional foods have the potentials to regulate sugar absorption and insulin level in the body (González-Montoya et al. 2018). T2DM account for 90% of all diabetes cases (DeFronzo et al. 2015). Following consumption of a carbohydrate rich diet, insulin secretion is stimulated by the combined actions of Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) on the pancreatic cells (Silveira et al. 2013). These incretins hormones perform their physiological roles through activation of their receptors. GLP-1 exhibits both insulinotropic and glucagonostatic effects that can normalize blood glucose levels in patients with T2DM (Deacon, 2018). As a metabolic regulatory mechanism, the biological activity of incretins is significantly reduced upon degradation by dipeptidyl peptidase IV (DPP-IV). Interestingly, inhibition of DPP-IV is considered a novel therapeutic strategy for managing T2DM (Deacon 2018; Mulvihill 2018). Food-derived DPP-IV-inhibitory peptides have been identified as natural alternatives to DPP-IV inhibitory compound (Nongonierma and FitzGerald 2015). Also, α-amylase and α-glucosidase inhibitors have been employed for the control of glucose homeostasis in diabetic patients (González-Montoya et al. 2018). Food-derived bioactive peptides are gaining interest from researchers owing to their antidiabetic properties and safety (Daliri et al. 2017). Some of the bioactive peptides with antidiabetic effects have been summarized in Table 6.

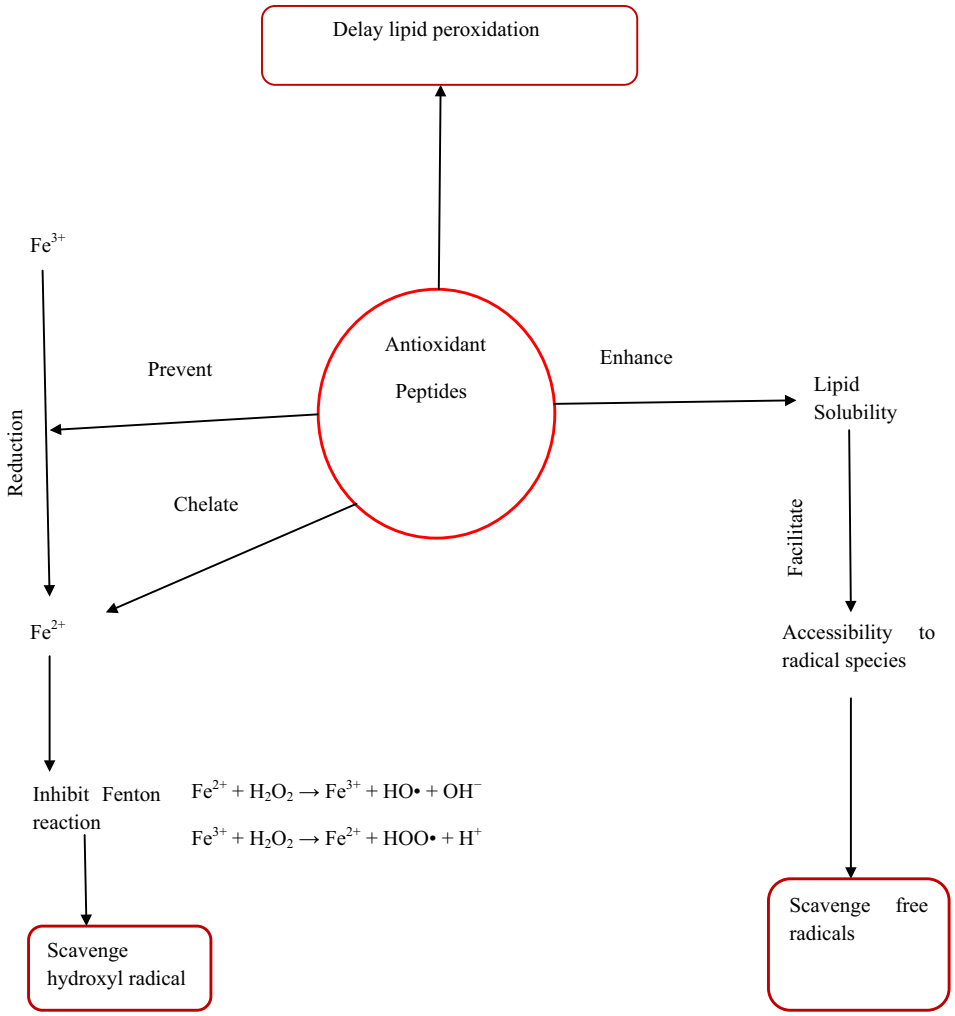

Fig. 4 Antioxidant peptides prevent fenton reaction, delay lipid peroxidation and enhance lipid solubility

Table 6 Antidiabetic peptides for T2DM

Bioactive peptide	Origin	Function	References
NNDDRDS,LSSTEAQQS,NAENNQRN, QQQQQGGSQSQ,EEPQQPQQ,IKSQSES	Germinated soybean	Inhibits DPP-IV, α-amylase and α-glucosidase	González-Montoya et al. (2018)
PPL	Meat protein	Inhibits DPP-IV	Lafarga and Hayes (2016)
YP, LP, IPI, VPL, IPA, IPAVF	Milk protein	Inhibits DPP-IV	Nongonierma and Fitzgerald (2015)
PGVGGPLGPIGPCTE,CAYNTERPVDRIR, PACCGPTISRPG	Tuna cooking juice hydrolysates	Inhibits DPP-IV	Huang et al. (2012)
GPAE, GPGA	Atlantic salmon skin gelatin	Inhibits DPP-IV	Li-Chan et al. (2012)
MHQPPQPL, AWPQYL,SPTVMFPPQSVL, VMFPPQSVL,AWPQYL, INNQFLPYPY	Goat milk casein	Inhibits DPP-IV	Zhang et al. (2015)
LKPTPEGDL, LPYPY, IPIQY, WR	Milk protein	Inhibits DPP-IV	Lacroix et al. (2017)
ILAP, LLAP, MAGVAHI	Macro alga (*Pamaria palmate*)	Inhibits DPP-IV	Harnedy et al. (2015)
IPA	Whey protein (β-lactosin)	Inhibits DPP-IV	Silveira et al. (2013)
IPAVF	Whey protein (β-Lg)	Inhibits DPP-IV	Tulipano et al. (2011)
VAGTWY	Whey protein (β-Lg)	Exhibits hypoglycemic effect	Uchida et al. (2011)
LPQNIPPL	Casein	Inhibits DPP-IV	Uenishi et al. (2012)
ILDKEGIDY,ILDKVGIQY,ILQLA,LLQLE AIR, LPVP, MPVQA, SPVVPF, TPVEPF	Camel milk protein	Inhibits DPP-IV	Nongonierma et al. (2018)
LAHKPL, ILDKEGIDY	Camel milk protein (α-lactalbumin)	Inhibits DPP-IV	Nongonierma et al. (2019)
VPV, YPI, VPF	Camel milk protein (β-casein)	Inhibits DPP-IV	Nongonierma et al. (2019
VPV	Camel milk protein	Inhibits DPP-IV	Nongonierma et al. (2019)
KDLWDDFKGL, MPSKPPLL	Camel milk protein	Inhibits DPP-IV	Mudgil et al. (2018)

Mechanism of Action of Antidiabetic Peptides

Many bioactive peptides have been demonstrated to exhibit antidiabetic effect through inhibition of DPP-IV as well as key enzymes linked to carbohydrates metabolism including α-amylase and α-glucosidase (Zhang et al. 2016). Previous study reported that fermented soybean protein contains low molecular weight peptides some of which induce insulin-stimulated glucose uptake in 3T3-L1 cells and antagonize PPAR-activities (Kwon et al. 2011). Similarly, AKSPLF, ATNPLF, FEELN, and LSVSVL peptides obtained from black bean protein hydrolysates possess glucose transporter-2 (GLUT-2) and sodium-dependent glucose transporter-1 (SGLT-1) inhibitory activity thereby reduce blood glucose level (Mojica et al. 2017). Salmon frame protein hydrolysates contain peptides promote glucose uptake in muscle cells (Roblet et al. 2016). Also, in related study, peptides (LPIIDI and APGPAGP) obtained from Silver carp protein hydrolysates effectively inhibited DPP-IV (Zhang et al. 2016) as presented in Table 6 (Fig. 5).

Antimicrobial Peptides and Their Mechanism of Action

Antimicrobial peptides are gaining interest because of their multifunctional properties including wound healing (Tomioka et al. 2014) and immunomodulation (Mansour et al. 2014) on a wide range of microorganisms (Memarpoor-Yazdi et al. 2012).These properties make antimicrobial peptides better alternatives against resistant pathogenic bacteria than conventional antibiotics (Daliri et al. 2017). Milk-derived peptides with antimicrobial property have been extensively studied (Piotto et al. 2012). Their antimicrobial activities are diverse, ranging from those that prevent the attachment or invasion of pathogen microorganisms, to those that inhibit microbial growth (Hernandez-Ledesma et al. 2014). In addition, peptide (ELLLNPTHQIYPVTQPLAPV) isolated from human colostrum inhibited bacterial growth by cell wall and cytoplasmic membrane destruction (Zhang et al. 2017). Also, AMPSSSEESII from β-s2–casein inhibit the growth of *Listeria innocua*, *Micrococcus luteus*, *Salmonella enteritidis* and *E. coli*. Milk-derived antimicrobial

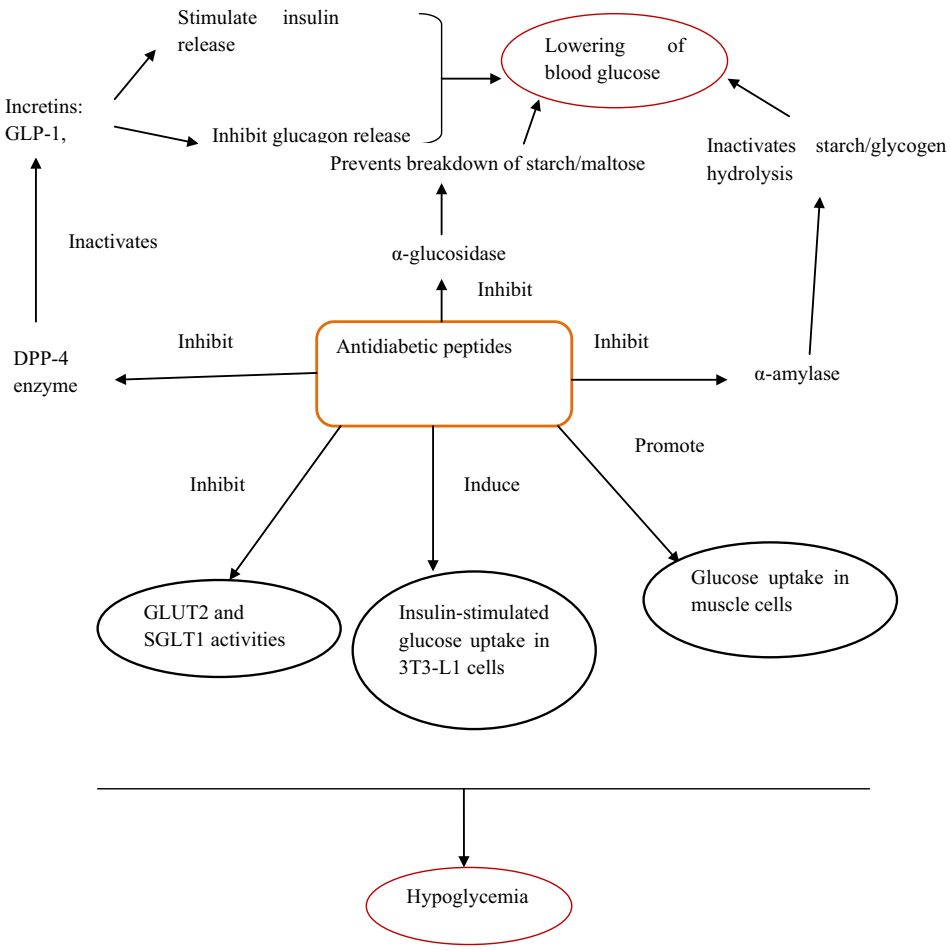

Fig. 5 Bioactive peptides exhibit antidiabetic effects

peptides contain more positively charged amino acid residues in their sequence (Guterstam et al. 2009). The net positive charge could aid binding to negatively charged bacterial membranes and arginine and lysine-containing peptides permeate cells by inducing ATP-dependent endocytic micropinocytosis (Guterstam et al. 2009). Besides, hydrolysis of bovine lactoferrin with pepsin and digestion of bovine whey proteins (β-lactoglobulin and α-Lactalbumin) produced antibacterial peptides with a broad spectrum against Gram-positive and Gram-negative bacteria (Pellegrini et al. 2001; Bellamy et al. 1992). Furthermore, biologically active peptide (SIFIQRFTT) has also been isolated from fish proteins with antimicrobial potentials against *Listeria innocua* and *Escherichia coli* (Guinane et al. 2015). Also, forage fish protein yielded GLSRLFTALK peptide which showed strong antimicrobial effects against S. *aureus*, *B. subtilis*, *S. pneumoniae*, *E. coli*, *S. dysenteriae*, *P. aeruginosa* and *S. typhimurium* (Ennaas et al. 2015). In some cultures and religion, consumption of blood is a taboo. However, in some countries, blood from domesticated animals is processed and consumed as food (Alan 2006). Hydrolysis of blood protein has also yielded several peptides with antimicrobial property. For examples, VNFKLLSHSLLVTLASHL peptide isolated from bovine haemoglobin effectively inhibited the growth of *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* (Aissaoui et al. 2016). In addition, hydrolysis of haemoglobin using pepsin enzyme yielded many peptides which effectively inhibited the growth of *Salmonella enteritidis*, *Escherichia coli*, *Shigella sonnei, Micrococcus luteus*, *Enterococcus faecalis*, *Listeria innocua*, *Staphylococcus saprophyticus*, *Bacillus cereus* and *Staphylococcus simulants* (Hu et al. 2011; Adje et al. 2013). Antimicrobial peptides possess both hydrophilic and hydrophobic amino acids at their terminals and this has been recognized as the major structural motifs through which they interact with microbes (Daliri et al. 2017). The mechanisms amongst which these bioactive peptides exert antibacterial effect can be either by making pores through the bacteria cell membrane or by interacting with macromolecules inside the microbial cells (Shah et al. 2016; Taniguchi et al. 2016). Researchers have discovered many antimicrobial peptides and these are available on database such as APD3 (Wang et al. 2016), CAMPR3 (Waghu et al. 2016) and YADAMP (Piotto et al. 2012). Antimicrobial peptides derived from food proteins are presented in Table 7.

Anticancer Peptides and Their Mechanism of Action

The orthodox drugs used for treatment and management of different forms of cancer are usually not effective and have adverse effects such as gonadotoxicity (Gutierrez et al. 2016), nephrotoxicity (Van Acker et al. 2016), neurotoxicity and cardiotoxicity (Oun et al. 2013). Consequently, researchers have intensified efforts towards investigation of

Table 7 Antimicrobial peptides derived from food proteins

Bioactive peptide	Origin	Function	References
ELLLNPTHQIYPVTQPLAPV	Human milk casein	Inhibits bacterial growth by cell wall and cytoplasmic membrane destruction	Zhang et al. (2017)
AMPSSSEESII	Human milk casein	Interacts with microorganisms to inhibit their growth	Zhang et al. (2017)
IKHQGLPQE	Milk protein	Inhibits the growth of pathogenic bacteria in infant formula	Kamali and Ehsani (2017)
SIFIQRFTT	Casein	Inhibits *Listeria innocua* and *Escherichia coli*	Guinane et al. (2015)
GLSRLFTALK	Atlantic mackerel (*Scomber scombrus*)	Interacts with microorganism to cause inhibition	Ennaas et al. (2015)
FPIGMGHGSRPA	Forage fish	Inhibits microbial growth	Tang et al. (2015)
VLSAADKGNVKAAWGKVGGH-AAEYGAEALERMF,ASHLPSDFTPA-VHASLDKFLANVSTVLTSKYR, VLSAADKGNVKAAWGKVGG-HAAEYGAEALERMFLSF	Bovine hemoglobin	Inhibits microbial growth	Hu et al. (2011), Adje et al. (2013)
VNFKLLSHSLLVTLASHL	Fish-by product	Inhibits the growth of *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus*	Aissaoui et al. (2016)
PGTAVFK EVSLNSGYY TTMPLW	Soy bean Barley α-casein	Causes bacteria and yeast membrane destruction	McClean et al. (2014)

food-derived bioactive peptides with anticancer properties with little or no side effects. Food protein-derived peptides possess inherent potentials for preventing different stages of cancer, including initiation, promotion, and progression (De Mejia and Dia 2010). The selectivity of action of anti-cancer peptides seems to be due to their strongly cationic character that allows them to interact with negatively charged structures on cancer cells, resulting in the destabilization of cancer cell membranes (Hoskin and Ramamoorthy 2008). Additionally, in vitro studies have shown that anti-cancer peptides act by inducing apoptosis, cell cycle arrest, modulating gene expression, and preventing angiogenesis (De Mejia and Dia 2010). In previous study, casein phosphopeptides (CPPs) inhibit proliferation of intestinal tumour HT-29 and AZ-97 cells and induce apoptosis by activating voltage-activated calcium channels, which mediate the calcium flux according to the depolarization state of the cell (Perego et al. 2012). Moreover, peptides from different sources have shown promising effects against cancer. For instance, oyster hydrolysate containing LANAK peptide and HVLSRAPR peptide isolated from *S. platensis* hydrolysate inhibited HT-29 cancer cell proliferation (Umayaparvathi et al. 2014; Wang and Zhang 2017). In addition, another peptide RQSHFANAQP from chickpea hydrolysate increased the level of p53 in breast cancer cell lines and inhibited their proliferation (Xue et al. 2015). Furthermore, setipinna taty-derived peptide (YALPAH) induced apoptosis in prostate cancer PC-3 cells (Song et al. 2014). Moreover, soybean protein hydrolysates contain many anticancer peptides exhibited strong antiproliferative effect against breast cancer cell line MCF-7 through induction of cell cycle arrest in S-phase and promote the expression of p21 and p27, decrease cyclin A expression, cleaved caspase 3, downregulate Bcl-2, PARP and caspase 9 expression with concomitant upregulation of p53 and Bax expression (Hung et al. 2014). In related study, peptides isolated from *Dendrobium catenatum* showed antiproliferative activity against HepG-2, SGC-7901 and MCF-7 cancer cells (Zheng et al. 2015) (Table 8).

Conclusion

Food-derived biologically active peptides have the inherent potentials to interact with tissues, cells, enzymes, reactive oxygen species and certain molecules to exert some therapeutic functions which are helpful in the management and treatment of many lifestyle-related diseases including hypertension, diabetes mellitus, obesity and cancer. In addition, several bioactive peptides possess antimicrobial effects owing to their multifunctional properties. However, the major challenge associated with bioactive peptides is retention of the activity after oral ingestion. Thus, the present

Table 8 Anticancer peptides

Bioactive peptide	Origin	Function	References
RHPFDGPLLPPGD RCGVNAFLPKSYL-VHFGWKLLFHFD KPEEVGGAGDRWTC	*Dendrobium catenatum*	Antiproliferative activity against HepG-2, SGC-7901 and MCF-7 cancer cells	Zheng et al. (2015)
KPEGMDPPLSEPED-RRDGAAGPK, KLPPLLLAKLLMSG-KLLAEPCTGR	Tuna cooking juice	Antiproliferative effect on breast cancer cell line MCF-7. Promotes the expression of p21 and p27, Decreases cyclin A expression, Cleaves caspase 3, Downregulates Bcl-2, PARP and caspase 9 expression, Upregulates p53 and Bax expression	Hung et al. (2014)
RKQLQGVN, GLTSK, GEGSGA, MPACGSS, LSGNK, MTEEY	Soybean protein	Effectively inhibits cell proliferation	Fernandez-Tomé et al. (2017), Vital et al. (2014)
YALPAH	Setipinna taty	Induces apoptosis in prostate cancer PC-3 cells	Song et al. (2014)
RQSHFANAQP	Chickpea	Increases the level of p53 in breast cancer cell lines and inhibits their proliferation	Xue et al. (2015)
HVLSRAPR	*S. platensis*	Inhibited HT-29 cancer cell proliferation	Wang and Zhang (2017)
LANAK	Oyster	Anticancer activity against human colon carcinoma (HT-29) cell lines	Umayaparvathi et al. (2014)
RRWQWR	Lactoferrin	Induces cytotoxicity via caspase-mediated and cathepsin B-mediated mechanism in T-leukemia cells	Arias et al. (2017)
PFWRIRIRR	Lactoferrin	Induces necrosis in leukemia cells (MEL and HL-60)	Arias et al. (2017)
FKCRRWQWRMKKLGAPSITCVRRAF	Lactoferrin	Inhibits leukemia cells	Arias et al. (2017)

review further highlighted the health promoting effects of food-derived bioactive peptides against chronic and degenerative diseases.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest with the contents of this article.

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