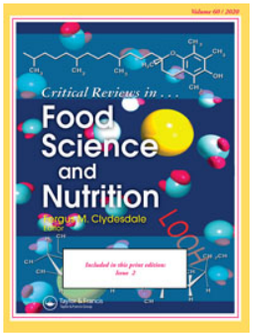

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REVIEW

Recently isolated antidiabetic hydrolysates and peptides from multiple food sources: a review

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ABSTRACT

Diabetes, a metabolic syndrome of global importance has been on a progressive rise in recent years. Several pharmacological approaches have been made, which have proved effective, but with underlying side effects. Bioactive hydrolysates (BHs) and peptides (BPs) from food sources, however, have shown the relative advantage of imparting less adverse effects. Furthermore, BHs and BPs from food have been discovered to impart their antidiabetic potentials through one or more mechanisms such as inhibition of digestive enzymes, inhibition of the antigenic enzyme – Dipeptyl peptidase IV (DPP-IV), decrease in blood glucose levels and increase in insulin uptake. Several plants and animal sources have been used as protein sources for the isolation of antidiabetic hydrolysates and peptides through different mechanisms and analytical techniques. This review integrates recent research information about several popular and unconventional food sources of BHs and BPs, their isolation techniques, antidiabetic effects and protein profiles. In addition, the fractionation technique(s) employed in each study and inhibition potentials of BHs and BPs are reviewed. This article is intended to supplement accessible scholarly literature and intellectual awareness on the subject of food-oriented approach for the management of diabetes.

KEYWORDS

Bioactive peptides; antidiabetic; bioactive hydrolysates; DPP-IV

Diabetes

Diabetes has been in existence since ancient times. In the first century, Aretaeus of Cappadocia (about 80–133 AD), a physician of Graeco-Roman origin named the disease from the Greek term *diabainein* meaning 'to go through'. In 1675, Thomas Willis (1621–1675), a British doctor added Mellitus; an adjectival phrase of Latin origin meaning 'honey-sweet' (Karamanou et al. 2016). Johann Peter Frank (1745–1821), a hygienist and German physician is credited for distinguishing diabetes mellitus (also called sugar diabetes) from diabetes insipidus, where an excessive amount of urine is produced as a result of a disturbance of the hormonal control of reabsorption of water in the kidneys (BACHEM Holding AG, 2017). Diabetes mellitus is known to be of two types. The Type I is insulin dependent and has a prevalence of about 5–10% originates from the inability of the pancreas to secrete insulin (blood sugar regulating hormone) due to the destruction of beta cells (Anguizola et al. 2013; Lauritano and Lanora, 2016; Kim 2014). Type II is non-insulin dependent and has a prevalence of about 90-95% is caused by the low production of insulin or the inability of the body to make use of the insulin produced. High BMI (Body mass index) values, sedentary lifestyle, aging and hereditary are factors known to have increased its incidence (Anguizola et al. 2013; Chiara and Adrianna 2016). People with Type I diabetes need regular dose of insulin administered via intravenous injection to lead their normal lives. Type II, which is more prevalent and consequently receives more attention is preventable. Statistical data from WHO shows a progressive rise in the prevalence of Type II diabetes mellitus (T2DM). In 1980, about 108 million (or 4.7% of the world's population) had T2DM; in 2014 the figure has progressively risen to an estimated 422 million (8.5%) (BACHEM Holding AG 2017).

Diabetes control mechanisms

Recently, there has been a considerable increase in the available medications for diabetes management. These include; Biguanides, Sulphonylureas, Meglitinides, Thiazolidinediones, DPP-IV inhibitors, GLP-1 receptor agonists, α-Glucosidase inhibitors, α-amylase inhibitors and SGLT-2 inhibitors (Kalita et al. 2018; Deacon, 2018). The peculiarity of sodium glucose-linked transporter (SGLT)-2 inhibitor, glucagon-like peptide (GLP)-1 receptor agonists and DPP-IV inhibitors among these therapies is the well-defined understanding of their working mechanisms. Though effective, these medications are known to trigger clinical symptoms and diverse side effects such as nausea, vomiting, weight gain, increase risk of cardiovascular

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disease, infection of the pancreas and cancer of the bladder (Chaudhury et al. 2017).

Bioactive peptides are one of the numerous options for pharmaceutical therapy of diabetes, administered orally or intravenously (Shaji and Patole 2008). Though somewhat less effective in action, food-derived peptides and hydrolysates possess the formidable advantage of having minimal side effects based on their natural sources and mechanisms of action (Li-Chan, 2015).

Peptides definition

Bioactive peptides are amino acids of short chain lengths of biological functionalities in the human body (Lima and Pedriali Moraes, 2018; Sanchez and Vazquez, 2017). They are also termed as cryptides (Udenigwe, 2014) which are protein fractions having health benefits beyond basic nutritional functionalities (Li-Chan, 2015). A peptide is only declared as bioactive when it is discovered to impart health benefit(s). Some known beneficial, desirable effects of bioactive peptides include; antimicrobial (Yang and Yousef, 2018), antioxidant (Hisham, Hiroki, and Takeshi 2018), antithrombotic (Chang et al. 2017), anti-hypertensive (Shobako et al. 2018), and immunomodulatory activities (López et al. 2016) amongst others.

Brief history of bioactive peptides

The study of bioactive peptides dates back to 1902 when Starling and Bayliss discovered a substance secreted from the intestinal lining with the potential of stimulating the secretion of digestive enzymes by the pancreas (Bayliss and Starling, 1902). The substance was named secretin and was found to be a peptide with its amino acid sequence determined. Several other peptides were discovered using a similar mechanism of purification and sequencing and the novel scientific concept of research was birthed (Schrader, Schulz-Knappe, and Fricker 2014). In 1950, bioactive peptides from a food source was first discovered by Mellender who found that phosphorylated casein peptides stimulated the bone calcification of rechetic infants without Vitamin D (Mellander, 1950). Over the years, a considerable amount of research has been made on the isolation of bioactive peptides from various food sources (Figure 1).

Isolation of bioactive peptides

Protein-rich foods are potential sources of bioactive peptides. Their natural supply, affordability and availability makes them better choices in selection of raw materials for the isolation of peptides. A systematic approach for production of bioactive peptides is given in Figure 2.

From a review of pertinent literature, common methods applied in the production bioactive peptides comprise of enzyme hydrolysis of food proteins, fermentation (Lee et al. 2017) or by chemical synthesis (which is mostly done for their purification and/or characterization). The research methodology of most studies has involved the isolation and

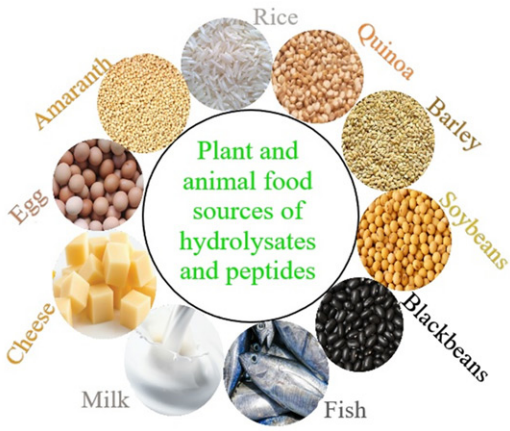

Figure 1. Multiple food sources for the isolation of bioactive hydrolysates and peptides.

identification of peptides from their natural food sources and a subsequent chemical synthesis of such peptides to obtain them in purer forms for more perfected characterization. (Uenishi et al. 2012; Connolly et al. 2017). In few situations however, water extracts of mushrooms and some plant parts have proven to be direct sources of bioactive peptides (Geng et al. 2016).

Common enzymes used for enzymatic hydrolysis include alcalase (Mojica, Luna-Vital, and Gonzalez de Mejia 2018), trypsin (Deng, Gruppen, and Wierenga 2018), pepsin (Bin et al. 2017), flavourzyme (Wang et al. 2015), and the SGID enzymes – trypsin and pancreatin (Oseguera-Toledo et al. 2016). Microbial fermentation as an isolation mechanism for peptides have involved proteolytic microbes like *Bacillus subtilis* and *Aspergillus oryzae* (Yang et al. 2012), *Lactobacillus plantarum* (Mechmeche et al. 2017) and *Mucor michei ex fries* (Hang and Zhao, 2012). Subsequent to the hydrolytic treatment is the fractionation, peptide sequencing and characterization. Fractionation is carried out to segregate the hydrolysates according to their molecular weights. Common examples of fractionation techniques include; ultrafiltration (Lin et al. 2012), ultracentrifugation (Velarde-Salcedo et al. 2013), RP-HPLC (Lacroix et al. 2017) and gel filtration chromatography (Jorge et al. 2015). Peptide sequencing and characterization involves the determination of the amino acid profile and the biological importance of the analyzed peptide. Inhibition potential of isolated peptides is commonly measured in terms of percentage inhibition or IC_{50} as shown in Tables 1–3.

Antidiabetic mechanisms of peptides

The *in vitro* and/or *in vivo* inhibition of enzymes such as DPP-IV, α-glucosidase and α-amylase involved in the increase in blood glucose level is the conventional approach in the determination of the antidiabetic potential of hydrolysates and peptides by researchers. Decrease in blood glucose level (Mojica, Luna-Vital, and Gonzalez de Mejia 2018), increased insulin production (for type 1 diabetes) or enhanced insulin sensitivity (Zhang et al. 2015) are alternative techniques for this.

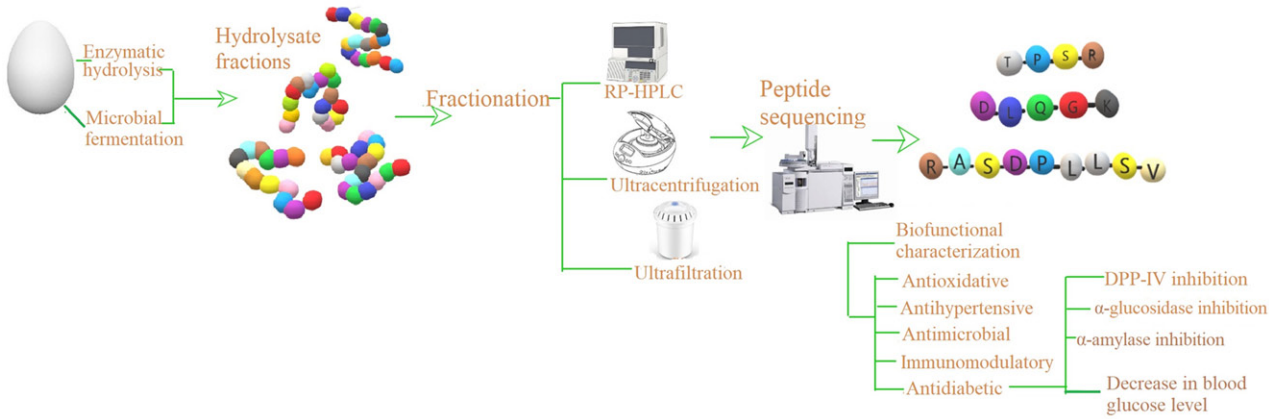

Figure 2. Flow diagram for the isolation and characterization of bioactive hydrolysates and peptides.

DPP-IV inhibition and GLP-1 receptor agonism are kn own to promote the synthesis of incretin hormones. DPP-IV is an enzyme which by the degradation of incretins, regulates glucose metabolism in the body (Zilleßen et al. 2016). Incretins, which include the GIP (glucose-dependent insulinotropic polypeptide, also termed as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1) are hormonal peptides released following ingestion of food with the fundamental purposes of regulating blood glucose levels and the inhibition of glucagon release by pancreatic cells (Farfan et al. 2016). Furthermore, the GLP-1 hormone retards the evacuation of the gastrointestinal contents, thereby prolonging the feeling of stomach satisfaction, reducing the desire for further food consumption and having an overall effect of body weight loss (Nauck and Meier, 2018). Inhibitors of the DPP-IV enzyme are understood to exert their functionalities by elevating the amounts of vital mode of endogenous GLP-1 with or without the contribution of other substrates such as GIP (Andersen, Deacon, and Holst 2018).

α-glucosidase is an enzyme ((EC 3.2.1.20), located in the intestinal brush border, chemically exocylclic, with the functionality of hydrolyzing 1,4-α-glycosidic linkages present in oligosaccharides, then converting them into monosaccharides absorbable from the intestine into the blood stream (Tania et al. 2017). The blood acts as the transporting medium for the newly synthesized monosaccharides as they get transported to their respective cells where they get converted into energy via the insulin conversion mechanism (Philip, 2012). By impeding the action of this enzyme, α-glucosidase inhibitors retard the digestion of complex carbohydrates thereby reducing the overall absorption of glucose in the blood and preventing hyperglycemia (Deacon, 2018).

α-Amylase (EC 3.2.1.1) is a digestive endoenzyme categorized as a member of the glycosyl hydrolase family with the basic function of catalyzing the hydrolytic breakdown of polysaccharides such as glycogen, starch (α-1,4-glycosidic linkages) and similar polysaccharides into products of lower molecular weights such as maltose, glucose, maltriose, etc. (De Souza and de Oliveira, 2010; Junying, Yu and Fuping, 2018). As one of the leading enzymes of carbohydrate digestion in the body, its inhibition would lead to an overall reduction in blood glucose levels (Chonlatid, Opeyemi, and Chitchamai 2018).

Several peptides and protein hydrolysates have been characterized from various food sources (Figure 1), but this review focuses on recently isolated ones with proven antidiabetic potentials.

In vitro investigations usually involve the use of biochemical assays of digestive enzymes for the evaluating the antidiabetic activities of BHs and BPs. In vivo studies have involved the use of human (Zhu et al. 2011) and laboratory rats as test subjects treated with specified doses of the isolated BHs and/or BPs with subsequent checks for effectiveness. Laboratory rats are usually induced with diabetes either by oral dieting or intravenous administration. Zhang et al. 2015 intravenously induced diabetes in laboratory rats using Streptozotocin and orally administered peptides enzymatically isolated from oats protein in dosages of 1.0, 0.5 and 0.25 g per kg of body weight in solutions bearing 0.6, 0.3 and 0.15 g/mL of the peptides. Their results showed that the antidiabetic activities of the peptides were more pronounced at higher doses. By elevating glycogenesis, enhancing the secretion of insulin, reducing food intake and improving insulin sensitivity. In preliminary studies carried out by the same researchers, the *in vitro* antidiabetic potentials of hydrolysates from the same food source was examined. A different antidiabetic mechanism was discovered involving the inhibition of α-glucosidase and consequently decreasing starch digestibility. Furthermore, the extraction procedures, fractionation techniques, antidiabetic mechanisms and general details about recently isolated peptides and protein hydrolysates with antidiabetic effects are discussed.

Animal sources of antidiabetic peptides

Dairy sources

Proteins from dairy sources (Table 1) are appraised as the most dominant sources of bioactive peptides (Ricci-Cabello, Olalla, and Artacho 2012). Bioactive peptides derived from milk are known to be versatile in health functionalities such as antimicrobial, antidiabetic, antithrombotic, antioxidant, and cholesterol-lowering (Korhonen and Pihlanto, 2007).

El-Sayed et al. 2016 investigated the antidiabetic potential of milk protein and its hydrolysate *in vivo* using diabetic

Table 1. Dairy sources of antidiabetic protein isolates, hydrolysates and peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification/ fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value		Reference
Milk protein and protein hydrolysate	Enzymatic	Trypsin	HPLC			Reduction in blood plasma glucose level *in vivo*			El-Sayed et al. 2016
Whey proteins	Enzymatic	Pepsin	Gel electrophoresis		1.0–26.6 kDa	DPP-IV and α-glucosidase inhibition	DPP-IV (IC_{50}) (mg/mL)	α-glucosidase (IC_{50}) (mg/mL)	Lacroix and Li-Chan, 2013
α-lactalbumin							0.036 ± 0.002	–	
β-lactoglobulin							1.279 ± 0.100	3.5 ± 0.04	
Lactoferrin							0.379 ± 0.035	–	
Bovine serum albumin							0.513 ± 0.056	–	
Whey protein isolate							0.075 ± 0.006	4.5 ± 0.60	
Dairy protein (Whey Protein Isolate WPI)	Enzymatic	Pepsin	Ultrafiltration			DPP-IV inhibition	IC_{50} (mg/mL) 0.075		Lacroix and Li-Chan, 2012
Whey proteins (β-lactoglobulin hydrolysates)	*In silico* analysis	BIOPEP database	Chemical synthesis	IPA		DPP-IV inhibition *in vitro*	Conc.(μm) 10 100	% inhibition 80-100 20-40	Tulipano et al. 2011
Milk Casein from Sheep	Enzymatic	Trypsin, Pepsin, Chymotrypsin				α-amylase inhibition *in vitro*	%inhibition for raw (H) after 240mins incubation	%inhibition for boiled (H) after 240mins incubation	Jan, Kumar, and Jha 2016
				Chymotrypsin Hydrolysates (CH)			38.69 ± 0.44	34.84 ± 0.44	
				Trypsin hydrolysates (TH)			35.16 ± 0.51	32.89 ± 0.65	
				Pepsin Hydrolysates (PH)			44.38 ± 0.59	39.62 ± 0.30	
Milk (β-Lactoglobulin)	Enzymatic Hydrolysis	Trypsin	RP-HPLC	VAGTWY	696.6Da	DPP-IV inhibition and glucose reduction *in vivo*	174μM		Uchida, Ohshiba, and Mogami 2011
Gouda Cheese			RP-HPLC			Reduction in glucose level *in vivo* and DPP-IV inhibition *in vivo* and *in vitro*	DPP-IV IC_{50} (μM)		Uenishi et al. 2012
				LPQNIPPL			4.6E + 01		
				LPQ			8.2E + 01		
				VPITPTL			1.1E + 02		
				VPITPT			1.3E + 02		
Milk proteins	Chemical synthesis		Reverse Phase- Ultra Performance Liquid Chromatography			DP P-IV inhibition *in vitro*	DPP-IV IC_{50} (mg/mL)		Nongonierma and FitzGerald, 2013
				EK			0.654 ± 0.001		
				GL			0.492 ± 0.115		
				AL			0.178 ± 0.014		
				VA			0.032 ± 0.001		
				WV			0.020 ± 0.001		
				FL			0.111 ± 0.003		
				HL			0.038 ± 0.001		
Milk proteins	Enzymatic hydrolysis	Pepsin and pancreatin	RP-HPLC			DPP-IV inhibition	Conc. (mg/mL)	IC_{50}(Basolateral solution after 2hrs)	Lacroix et al. 2017
				LKTPEGDL			12.5	18 ± 2	
				LPYPY			75	12 ± 4	
				IPIQY			50	15 ± 3	

(*continued*)

Table 1. Continued.

Source	Extraction method(s)	Extraction tool	Separation/ purification/ fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value		Reference
				IPI			12.5	14 ± 5	
				WR			75	46 ± 8	
				WPI digests			62.5µg/mL	12 ± 3	
Whey Protein Concentrate rich in Bovine β-Lactoglobulin	Enzymatic hydrolysis	Trypsin	Semi preparative RP-HPLC			DPP-IV inhibition *in vitro*	IC_{50} (µM)		Silveira et al. 2013
				IPVAF			44.7 ± 3.6		
				TPEVDDEALEK			319.5 ± 4.0		
				IPAVFK			143.0 ± 1.3		
				VLVLDTDYK			424.4 ± 31.5		
Bovine Whey Protein Isolate and α-Lactoglobulin	Enzymatic Hydrolysis	Pepsin				DPP-IV inhibition *in vitro*	IC_{50} (µM)		Lacroix and Li-Chan,2014
				WLAHKALCSEKLDQ	838.02		141		
				LAHKALCSEKL	1212.47		165		
				TKCEVFRE	1011.16		166		
				LCSEKLDQ	935.06		186		
				LKPTPEGDL	969.1		45		
				LKPTPEGDLEIL	1324.54		57		

rats. Experimental rats were grouped and orally administered with a daily dosage 800 mg/kg of body weight with the hydrolysates and milk protein in their respective groups for a period of 6 weeks. Their study proved that oral administration of milk proteins (MP) or milk protein hydrolysates (MPH) by the rats significantly reduced the blood glucose level, total lipids of blood plasma, including; low density lipoproteins (LDL), very low density lipoproteins (VLDL), triglycerides and total cholesterol, in rat plasma, thus confirming that MP and MPH could be used as anti-diabetic agents.

Lacroix and Li-Chan (2013) researched on the inhibition of the enzymes DPP-IV and α-glucosidase by pepsin-treated whey proteins. Hydrolysates of whey protein isolates produced by digestion with peptic enzyme were explored for their functionalities as α-glucosidase and DPP-IV inhibitors. Their results revealed that α-lactalbumin hydrolysate, of all hydrolysates produced, displayed the greatest potential with an IC_{50} value of 0.036 mg/mL. They also discovered that only α-lactalbumin, WPI and *β*-lactoglobulin, and hydrolysates showed some inhibitory strength in opposition to α-glucosidase.

The octapeptide LPQNIPPL, along with 46 others were isolated and identified from casein in the water-soluble extract (ripened for a 12 month period) of a guoda-type cheese by Uenishi et al. 2012. Their DPP-IV inhibitions were determined *in vivo* along with their individual impact on the blood glucose level of the laboratory rats. The peptide was dissolved in 20% glucose solution having a concentration of 60 g/mL and orally administered to the experimental rats at 0.5mL per rat and blood glucose level checked after 0, 15, 30, 60 and 120 mins interval. The peculiarity of the octapeptide amongst others was its display of the strongest DPP-IV inhibition (IC_{50} of 46 µM) and its quantitative increase during the ripening process.

A study conducted by Lacroix and Li-Chan (2012) involving protein isolates of four different dairy products including sodium caseinate, whey protein isolate, skim milk powder and milk protein concentrate. The study involved digestion of all the dairy products with gastrointestinal enzymes and treatment of only sodium caseinate and whey protein isolate with 11 different proteases. Their investigation showed that of all preparations, the peptic digestion of WPI had the highest DPP-IV inhibition with 0.075mg/mL IC_{50} value. Similarly, Silveira et al, 2013 conducted a similar study using enzymatic digestion with trypsin. Fractionation was then carried out using a chromatographic separation at semi preparative scale. Their results also further confirmed that *β*-lactoglobulin would be beneficial ingredients of foods against type 2 diabetes.

In a study performed by Uchida, Ohshiba, and Mogami (2011), beta-lactoglobulin treated with trypsin produced the antidiabetic peptide VAGTWY which significantly reduced the glucose level of mice. Rats were orally administered at a dosage of 300 mg/kg equivalent to 0.1mL/10g of body weight and their blood glucose level checked after every 30mins for a 120mins period. Their readings showed a significant decrease in the level of blood glucose.

Table 2. Egg-related sources of antidiabetic peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification/ fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value		Reference
Egg white protein	Enzymatic	Alcalase	HPLC	RVPSLM TPSPR DLQGK AGLAPY RVPSL DHPLFLF HAEIN QIGLF		α-amylase and α-glucosidase inhibition *in vitro*	α-amylase (IC_{50}) >150μmol/L	α-glucosidase (IC_{50}) 23.07 μmol/L 40.02 μmol/L >150 μmol/L	Yu et al. 2011
Egg yolk protein by-product	Enzymatic	Proteinase from *C. ficifolia Asian pumkin* pulp	Chemical synthesis	RASDPLLSV RNDDLNYIQ LAPSLPGKPKPD AGTTCLFTPLAL-PYDYSH		α-glucosidase and DPP-IV inhibition *in vitro*	α-glucosidase – – 1065.6μmol/L –	DPP-IV(μmol/L) 426.25 350–400 361.5 –	Zambrowicz et al. 2015a
Egg Yolk Protein	Enzymatic hydrolysis	Pepsin	Exchange chromatography and RP-HPLC	YINQMPQKSRE YINQMPQKSREA VTGRFAGHPAA-Q		DPP-IV and α-glucosidase inhibition *in vitro*	DPP-IV IC_{50} (μg/mL) 222.8 355.8 1402.2	α-glucosidase IC_{50} (μg/mL)) 1694.3 454.6 365.4	Zambrowicz et al. 2014b

Table 3. Marine sources of antidiabetic hydrolysates and peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification/ fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value	Reference
Wild marine fish	Enzymatic	Mixture of 25% pepsin, 35% trypsin, 35% chymotrypsin, 5% pancreatic lipase	Filtration through ceramic membranes (200μm)	Marine collagen peptides	130–3000 Da	Decrease in blood fasting glucose level and blood fasting insulin level of diabetic patients.		Zhu et al. 2010
Fish skin gelatin (Halibut, Tilapia,Hake and Milkfish)	Enzymatic	Flavourzyme from *Aspergillus oryzae*	Ultrafiltration	Halibut SPGSSGPQGFTG GPVGPAGNPGAN-GLN PPGPTGPRGQPNI-GF Tilapia IPGDPGPPGPPGP LPGERGRPGAPGP GPKGDRGLPGPP-GRDGM	 862.32 1021.42 1261.44 919.53 1026.58 1358.76	DPP-IV inhibition (*in vivo* and *in vitro*), enhancement of GLP-1 and insulin secretion *in vivo*	DPP-IV(μM) 101.6 81.3 146.7 65.4 76.8 89.6	Wang et al. 2015
Goby fish protein	Enzymatic	*B. mojavensis* (A21) and Alkaline protease extraction from trigger fish intestine		Hydrolysates from treatments with *B. mojavensis* A21 proteases and triggerfish crude alkaline proteases.		Decrease in serum glucose level, α-amylase activities and hepatic glycogenesis *in vivo*		Nasri et al. 2015
Salmon Skin Gelatin	Enzymatic hydrolysis	Alcalase (ALA) Bromelain (BRO) Flavourzyme (FLA)	Fractionation by Ultrafiltration and purification by HPLC	GPAE GPGA	300.4Da 372.4Da	DPP-IV inhibition *in vitro*	IC_{50} (μM) 49.6 41.9	Li-Chan et al. 2012
Tuna cooking juice	Enzymatic	Orientase (OR) and Protease XXIII (PR)	Gel filtration and HPLC	PACGGFYISGRPG CAYQWGRPVNRIR PGVGGPMGPIGP-CYQ	1304.6 Da 1690.8 Da 1412.7 Da	DPP-IV inhibition *in vitro*	IC_{50} (μM) 96.4 78.0 116.1	Huang et al. 2012

Nongonierma and FitzGerald (2013) evaluated the DPP-IV inhibition potential of 12 different bioactive peptides derived from milk proteins. Only 8 peptides namely GL, AL, VA, WV, FL, HL, SL, and IP were found to possess inhibitory potentials. Results obtained showed that the WV peptide had the only noncompetitive, highest potential with an

IC_{50} value of 65.69 ± 2.95 µM; its inverse VW, however, displayed no inhibition.

With the in-silico approach, Tulipano et al. 2011 were able to show that the tripeptride IPA obtained from whey proteins possesses the DPP-IV inhibition potential.

Egg

Egg has its protein in the egg white and yolk. The proteins obtained from hen eggs, predominantly comprise of ovotransferrin (Giansanti et al. 2012), ovalbumin, ovomucin (Stadelman and Cotterill, 2001), ovomucoid (Nolan et al. 2000), lysozyme (Alderton, Ward, and Fevold 1945), avidin, cystatin, ovoinhibitor (Nolan, Phillips, and Mine 2005), lipoprotein and glycoprotein (Omana, Wang, and Wu 2010).

In an extensive study on egg composition conducted by Nolan, Phillips, and Mine (2005), based on relative abundance, egg proteins are classified as major; Ovalbumin (54%), ovotransferrin (12%), ovomucoid (11%), ovomucin (3.5%) and lysozyme (3.5%), and minor; avidin (0.05%), ovomacroglobulin (0.5%) and cystatin (0.05%).

Egg is also known to be a functional food rich in protein of high biological value (Surai and Sparks, 2001) from which several bioactive peptides (Table 2) can be derived. These proteins and peptides have been discovered to impart their functionality either in the raw form or when hydrolyzed *in vivo* or *in vitro* (Hartmann and Meisel, 2007). Egg peptides are known to possess anticancer, antimicrobial (Yazdi, Asoodeh, and Chamani 2012), antioxidant (Carrillo et al. 2016), antihypertensive (Majumder et al. 2013), antidiabetic (Yu et al. 2011) and bone growth promotion (Eckert et al. 2013).

In a research conducted by Yu et al. (2011) the peptides RVPSLM and TPSPR were isolated from egg white hydrolysate via enzymatic hydrolysis with alcalase and found to be effective (IC_{50} values of 23.07 and 40.02µmol/L) in inhibiting the enzyme α-glucosidase and thus of functional antidiabetic activity. Other peptides isolated in the course of the study include DLQGK, AGLAPY, RVPSL, DHPLFLF, HAEIN and QIGLF and examined for α-amylase inhibition but none was found to show any inhibition (IC_{50} >150g/mol).

Using egg yolk by-product as the protein source, Zambrowicz et al. (2015b), isolated multifunctional novel peptides of antioxidative and antidiabetic potentials. They found that the peptides: RASDPLLSV, RNDDLNYIQ and LAPSLPGKPKPD showed significant DPP-IV inhibition with IC_{50} values ranging from 361.5 to 426.25 µmol/L. LAPSLPGKPKPD in particular was found to have an additional α-glucosidase inhibitory potential with IC_{50} value of 1065.6 sµmol/L.

Nongonierma and FitzGerald, (2014) developed an *in silico* model to estimate the DPP-IV inhibition capability of 72 dietary proteins from various sources. Their calculations showed that chicken egg ovomucoid has a relatively lower potency index (PI) of chicken egg 0.13×10^{-6} µ/Mg in comparison with 17.89×10^{-6} µ/Mg from bovine κ-CN. Chicken egg ovotransferrin was calculated to have a PI $>5.00 \times 10^{-6}$ µ/Mg.

Marine

Marine foods are rich sources of proteins and bioactive peptides (Table 3) with cosmeceutical, pharmaceutical and nutraceutical functionalities (Venkatesan et al. 2017). Such peptides have been discovered to exhibit versatile bioactivities such as antihypertensive, antioxidant, antioxidative, antimicrobial, antidiabetic and neuroprotective effects (Cheung, Ng, and Wong 2015). A slight number of fish protein hydrolysates have manifested the activity of stimulating glucose uptake *in vivo* and are applicable to the management of hyperglycemia in addition to methodical therapy. These hydrolysates can alleviate glucose tolerance either by inciting glucose uptake through a mechanism contrary to that of insulin or by raising insulin responsiveness in target cells (Cheung, Ng, and Wong 2015). Collagen, for example, is an abundant protein that can be extracted from common fish by-products such as skin, scales and bones (Venkatesan et al. 2017) which has been used extensively in the manufacture of antidiabetic pharmaceuticals (Lauritano and Ianora, 2016).

Zhu et al. 2010 previously examined the therapeutic effects of marine peptides enzymatically derived from fish hydrolysates administered on 100 Chinese patients with type 2 diabetes mellitus. The enzymatic digestion employed the use of composite proteases such as chymotrypsin (35%), trypsin (35%), pepsin (25%), and pancreatic lipase (5%). Oral administration of a 6.5 g mixture of marine collagen peptides and carboxymethylcellulose (as placebo) in water twice daily (ahead of bedtime and breakfast) for a 3-month experimental period. After 1.5 and 3 months of the administration, they found that there was a remarkable fall in the fasting blood insulin levels, blood fasting glucose levels and total cholesterol levels with a corresponding increase in insulin sensitivity index and high-density lipoprotein (HDL) levels. In a research conducted by Li-Chan et al. (2012) regarding the isolation of DPP-IV inhibitory peptides from Atlantic salmon skin gelatin using three enzymes, namely; flavourzyme (EC 3.4.11.1), bromelain (EC 3.4.22.33) and alcalase (EC 3.4.21.62) with varying enzyme/substrate ratios (ESRs) of 6, 3, 2 and 1% respectively. The inhibitory potential of the hydrolysates from each enzymatic treatment was evaluated and the flavorzyme hydrolysate with 6% ESR was sound to have the highest inhibition. Fractionation by ultrafiltration and further isolation by HPLC led to the identification of two peptides with amino acid sequences of GPAE and GPGA. The peptides were found to have molecular weights of 372.4 and 300.4 Da with IC_{50} values of 49.6 and 41.9µM for dose-dependent DPP-IV inhibition respectively.

Wang et al. 2015 in a research study compared the DPP-IV inhibition of hydrolysates enzymatically isolated from the skin gelatin of warm water (Tilapia) and cold water (Halibut) fishes. Results from in vitro studies showed that Tilapia hydeolysates had better DPP-IV inhibition (51.9%) relative to Halibut (38.2%). In vivo studies confirmed this

trend with more effectively. Laboratory rats were induced with diabetes by a one-time peritoneum injection of Streptozotocin and treated with a daily dosage of 750 mg/kg dosage of the prepared hydrolysates for a 30-day period. Subsequently, the GLP-1 levels, insulin levels and DPP-IV activity of the blood plasma of the rats were examined and the Tilapia hydrolysates were found to impart more positive changes. The halibut skin gelatin hydrolysates include SPGSSGPQGFTG, GPVGPAGNPGANGLN and PPGPTGPRGQPNIGF with IC_{50} values of 101.6, 81.3 and 146.7 μM respectively. The Tilapia skin gelatin hydrolysates include IPGDPGPPGPPGP, LPGERGRPGAPGP and GPKGDRGLPGPPGRDGM with IC_{50} values of 65.4, 76.8 and 89.6 μM respectively. As shown in their results, it was found that the warmblooded fish gelatin skin (Tilapia) has a higher antidiabetic potential.

In another study conducted by Nasri et al. (2015) to investigate the antidiabetic capabilities of hydrolysates and the raw, undigested goby fish muscle proteins in vivo. In their research, diabetes was induced in rats through a diet rich in fructose and fat and subsequently administered with an average, daily dosage of 400 mg of the hydrolysates prepared from enzymatically digested goby fish protein for a 10-week period. They found that these hydrolysates are very effective in controlling diabetes by decreasing the blood glucose levels, α-amylase activity and hepatic glycogen levels.

Several peptides of various functionalities have been synthesized using tuna cooking juice as the protein source. Such peptides have been found to possess antioxidative (Hsu, Lu, and Jao 2009), anticancer (Huang et al. 2014) and DPP-IV inhibition (Huang et al. 2012) potentials. Huang et al. (2012) conducted a study to determine the potential of peptides enzymatically isolated from tuna cooking juice (5.44% protein content) in inhibiting DPP-IV. The enzymes orientase (OR) and Protease XXIII (PR) were used and three peptides which showed dose-dependent DPP-IV inhibition were isolated. Three peptides PACGGFYISGRPG (1304.6 Da) CAYQWGRPVNRIR (1690.8 Da) and PGVGGPMGPIGPCYQ (1412.7 Da) were isolated and found to possess DPP-IV inhibitory potential with IC_{50} values of 96.4 μM, 78.0 μM and 116.1 μM, respectively. Following their enzymatic isolation, simulated gastrointestinal digestion (SGID) was also carried out to check its effect on the DPP-IV inhibition functionality of the peptides. Their results showed that the functionality was secured or even enhanced following the SGID treatment.

Plant sources

Cereals and pseudocereals

Proteins from cereal-food sources contribute the larger fraction of the globally consumed dietary protein, especially for developing countries where wheat and rice are staple sources of plant protein (van der Spiegel, Noordam, and van der Fels-Klerx 2013; Shewry and Halford, 2002). The nomenclature cereal originates from the Latin word cerealis, which means grains. Botanically, it is categorized as a fruit type termed caryopsis, comprising of the bran, germ and endosperm (Sawar et al. 2013). More precisely, cereals are defined as edible grains or seeds belonging to the grass family (McKevith,2004) or food products processed from their starchy grains (Sawar et al. 2013). The protein content in cereals ranges from 6-15% with a larger fraction located in the storage proteins (Shewry and Halford 2002). The prominent storage protein(s) vary with the cereal type, but general examples include glutelins (wheat, barley and rice), prolamins (maize), globulins (oats), thionin (rye and oat) and germins (wheat and barley) (Kulp and Ponte 2000; Cunsolo et al. 2012).

Pseudocereals are non-grassy, plant-based foods with similar composition and functionalities with cereals. However, they differ in their number of seed leaves (cotyledons) with two seed leaves (dicotyledons) as opposed to true cereals with one (monocotyledons) (Alvarez-Jubete, Arendt, and Gallagher 2010). Common examples include quinoa, buckwheat and amaranth.

Cereals and pseudocereals are potential plant sources of peptides (Table 4) with health promoting benefits (Malaguti et al. 2014). Lunasin, a bioactive peptide with a 43 amino acid (SKWQHQQDSCRKQKQGVNLTPCEKHIMEKIQGR GDDDDDDDDD) peptide chain length was initially isolated from soyabean (Park, Jeong, and de Lumen 2005) and later from cereals such as; rye, barley, wheat and rice and amaranth, a pseudocereal (Jeong et al. 2007; Jeong et al. 2009, Jeong et al. 2010). This peptide was reviewed by Hernandez-Ledesma, Hsieh, and de Lumen (2013) to have antioxidative protection effects on DNA and the potential of terminating proliferative cell multiplication of cancer cells.

Rice

In a study aimed at optimizing the production mechanism of a DPP-IV inhibitor peptide from defatted rice bran as protein source using two commercially available enzymes, Hatanaka et al 2012 discovered that the enzyme, Umamizyme G, synthesized peptides which proved to be 10 times more potent in the inhibition of DPP-IV (with an average IC_{50} value of 2.3 ± 0.1 mg/M) relative to the peptides synthesized using the Bioprase SP enzyme.

Hatanaka et al 2015 conducted a study on the evaluation of the antidiabetic functionality of peptides from two rice products – rice bran and sake lees enzymatically digested with a commercially available protease – Denazyme AP derived from *Aspergillus oryzae*. Their findings revealed that the hydrolysate produced from the bran had higher DPP-IV inhibition with an IC_{50} value of 1.28 ± 0.18 mg/ml in comparison with the hydrolysate from sake lees which displayed a relatively lower inhibition bioactivity with an IC_{50} value of 27.55 ± 5.76 mg/ml.

Brewers spent grain

Brewer's spent grain, which represents about 85% of the overall by-products occupies the largest fraction of by-products obtained during beer-brewing (Mussatto, 2014; Xiros and Christakopoulos, 2012). It is usually obtained from

Table 4. Cereal and pseudocereal sources of antidiabetic hydrolysates and peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification /fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value			Reference
Defatted rice bran	Enzymatic	Umamienzyme G (UG) and Bioprase SP (BSP)	Gel filtration chromatography	UG peptides BSP peptides		DPP-IV inhibition *in vitro*	IC_{50} (mg/mL) 2.3 ± 0.1 26.4 ± 2.3			Hatanaka et al. 2012
Rice bran protein and Sake lees	Enzymatic	Denazyme AP protease from *Aspergillus oryzae*	Gel filtration chromatography	Rice protein hydrolysate Sakelees hydrolysate		α-glucosidase and DPP-IV inhibition *in vitro*	α-glucosidase – –	DPP-IV IC_{50} (mg/mL) 1.45 ± 0.13 1.28 ± 0.18		Hatanaka et al. 2015
Brewers' spent grain	Enzymatic	Alcalase, SGID	Membrane fractionation and RP-HPLC	BSG hydrolysate ILDL ILLPGAQDGL		DPP-IV inhibition *in vitro*	IC_{50} 3.57 ± 0.19 mg/mL 1121.1μM 145.5μM			Connolly et al. 2017
Brewers' spent grain	Enzymatic	Alcalase	Ultrafiltration	BSG hydrolysate		α-glucosidase inhibition *in vitro*	At concentration of 4.0mg/mL inhibited 21.42% α-glucosidase			Lin et al. 2012
Amaranthus grain	Enzymatic	Alcalase	Gel filtration	Albumin hydrolysate fraction after 48 hrs (AHF48) Globulin hydrolysate fraction (GBHF48) Glutelin hydrolysate fraction (GLHF48)		DPP-IV inhibition *in vivo*	Fraction 2nd AHF48 3rd AHF48 3rd GBH48 4th GBH48 2nd GLH48 3rd GLH48	IC_{50} (mg/mL) 8.34 ± 0.09 1.98 ± 0.01 5.6 ± 0.1 0.25 ± 0.04 1.95 ± 0.08 0.12 ± 0.006		Jorge et al. 2015
Amaranth seed	Enzymatic, SGID	Trypsin, trypsin-pancreatin mixture	Ultrafiltration and ultracentrifugation	STHASGFFFFHPT STNYFLISCLLFVL-FNGCMGEG GLTEVWDSNEQEF	1482.6 Da 2428.7 Da 1553.6 Da	DPP-IV inhibition *in vitro*				Velarde-Salcedo et al. 2013
Quinoa protein	SGID	Pepsin and pancreatin	Ultrafiltration and RP-HPLC	IQAEGGLT DKDYPK GEHGSDGNV	787.4 764.4 870.4	DPP-IV, α-amylase, α-glucosidase inhibition *in vitro*	%DPP-IV inhibtn at 250μM 17.05 ± 0.06 – –	%α-amylase inhibtn at 250μM – – 6.86 ± 0.16	%α-glucosidase inhibtn at 250μM 55.85 ± 0.26 22.16 ± 0.6 30.84 ± 0.69	Vilcacundo, Villaluenga and Ledesma (2017)
Quinoa	Enzymatic	Papain and papain-like enzyme	Gel Permeation - High Performance Liquid Chromatography (GP-HPLC)	Quinoa protein hydrolysates from Papain enzyme (QPH-P) Quinoa protein hydrolysates from Papain-like enzyme (QPH-PL)		DPP-IV inhibition *in vitro*	IC_{50} (mg/mL) 0.88 ± 0.05 0.98 ± 0.04			Nongonierma et al. 2015

Oats Protein	Enzymatic hydrolysis	Alcalase	Ultrafiltration	FLQPNLDEH DLELQNNVFPH TPNAGVSGAAAG-AGAGGKH	556.757 663.32 711.	Increased insulin secretion and sensitivity, lowering of blood glucose *in vivo*			Zhang et al.2015
Cummin seeds (*Cuminum cyminum*)	Enzymatic Hydrolysis	Commercial enzyme Protamex	Gel Elution Liquid Fraction Entrapment Electrophoresis (GELFREE)	FFRSKLLSDGAAA-AKGALLPQYW RCMAFLLSDGAA-AAQQLLPQYW DPAQPNYPWTAV-LVFRH		α-amylase inhibition *in vitro*	IC_{50} (μM) 0.04 0.002 0.05		Siow and Gan,2016

barley which is the raw material commonly used for beer production (Lynch, Steffen and Arendt, 2016). Connolly et al. (2017) isolated DPP-IV inhibitory peptides from protein-enriched brewer's spent grain isolate hydrolyzed using alcalase enzyme (EC 3.4.21.62). Following the enzymatic digestion which occurred for a 240 minutes' time period, the IC_{50} value for DPP-IV inhibition was determined to be 3.57 ± 0.19 mg/ml. After each sequential treatment of ultrafiltrative fractionation, simulated gastrointestinal digestion and RP-HPLC, the value for DPP-IV inhibition was checked. Their results showed that ultrafiltration had no significant effect on the inhibition potential. Further exposure of the alcalase hydrolysate to simulated gastrointestinal digestion effected an increase in the DPsP-IV inhibition activity. They reported that following the fractionation of the hydrolysates using (RP-HPLC), the 28th fraction displayed the highest DPP-IV inhibition. The novel peptides ILLPGAQDGL and ILDL with DPP-IV inhibition IC_{50} values of 145.5 and 1121.1 μm were discovered within the fraction.

Lin et al. (2012) in a study involving the optimization of the enzymatic hydrolysis of proteins extracted from brewer's spent grain by alcalase also investigated the *in vitro* inhibition of the hydrolysate obtained against α-glucosidase enzyme. Their findings showed that at a concentration of 4.0 mg/mL, α-glucosidase inhibition of 21.42% was achieved. Their study also showed that purification by ultrafiltration had a relatively higher inhibition in comparison to purification without ultrafiltration. The overall fraction of the protein hydrolysate with molecular weight not up to 5 kDa was discovered to have an inhibition of 56.41%.

Amaranth

Amaranth grain proteins including glutelins, globulins and albumin were extracted and enzymatically hydrolyzed using alcalase enzyme (EC 3.4.21.62) by Jorge et al. 2015. The hydrolysates obtained were then fractionated through gel filtration and their inhibition potentials against DPP-IV by oral administration to diabetic mice were evaluated. The third fraction of the glutelin hydrolysates named as GluIII showed the highest DPP-IV inhibition with IC_{50} value of 0.12 ± 0.006 mg/mL. Other hydrolysate fractions which displayed strong inhibition include globulin hydrolysate G.IV and albumin hydrolysate A.III with IC_{50} values of 0.25 ± 0.04 and 1.98 ± 0.01 mg/ml respectively. Velarde-Salcedo et al. (2013) in a study regarding the potential of peptides obtained from Amaranthus protein hydrolysis to inhibit DPP-IV *in vitro* discovered that peptides contained in all protein fractions obtained from amaranth possess the potential to inhibit the DPP-IV enzyme. In their study, albumins, globulins (7S and 11S), and glutelins were enzymatically digested with trypsin. Peptides released were then examined for their potential to inhibit DPP-IV. Their results showed that the glutelins fraction displayed the strongest inhibition potential and the weakest by the 11S globulins proteins.

Quinoa

Quinoa is described as a pseudo-cereal consumed by the South American Andean culture basically as a staple food. Quinoa seeds are of high protein content of about 12-19%, making them one richest sources of high biological value protein among other known grain crops (Przybylski, Chauhan, and Eskin 1994). Quinoa proteins, in addition to their high nutritional value have been found to possess some health benefits and also as a potential source of biologically functional peptides Aluko and Monu (2003).

Vilcacundo, Villaluenga and Ledesma (2017) conducted a study on the release of antidiabetic peptides from quinoa by a simulated gastrointestinal digestion, *in vitro*. The antidiabetic activities of the isolated peptides were evaluated on their inhibition of α-amylase, α-glucosidase and DPP-IV enzymes following the gastrointestinal digestion. Fractionation of the peptides by ultrafiltration occurred and the inhibitory potential of the fractioned peptides were also evaluated. Results were represented as D0- digestion starting point, GD120- gastric digest obtained after incubating with pepsin for 120 min, ID60 and ID120 representing digests after 60 min incubation with pepsin and 120 min incubation with pancreatin respectively. Their results showed that fractionated peptide with molecular weight less than 5 kDa had the highest α-glucosidase inhibition with IC_{50} (mg protein/ml) value of 1.45 ± 0.12 and ID120 had the lowest inhibition (1.81 ± 0.03). ID120 showed the strongest inhibition for α-amylase with an IC_{50} value of 0.19 ± 0.02 and ID60 peptide wit molecular weight less than 5 kDa had the weakest inhibition of 1.09 ± 0.04 IC_{50} value. Of all peptides isolated, only the D0 peptide showed no inhibition for DPP-IV. The ID60 peptide showed the strongest inhibition with IC_{50} value of 0.23 ± 0.01 and the GD120 value showed the weakest inhibition of 2.52 ± 0.06 IC_{50} value.

Protein isolated from quinoa was enzymatically hydrolyzed with two different enzymatic preparations viz papain (3.4.22.2) and its microbial derivative by Nongonierma et al. (2015). The DPP-IV inhibition potential of the hydrolysates from both preparations were examined with the protein isolate as control. They reported that the protein isolate had higher inhibition while both enzymatic preparations had similar inhibition capacities with similar IC_{50} values of 0.88 ± 0.05 mg/ml.

Legumes

Beans

Common beans are a rich source of bioactive peptides (Table 5) and other biologically active compounds such as polysaccharides, oligosaccharides and polyphenols (Luna-Vital et al. 2015). As potential sources of protein, they have a high protein content ranging from 16 to 32% with lectin and phaseolin having a larger fraction (about 50–70%) of the total protein content (Campos-Vega et al. 2009). Luna-Vital et al.s (2015) characterized bioactive peptides derived from beans protein and found them to have antioxidant, antidiabetic, antihypertensive, metal chelating and anti-inflammatory potentials.

Mojica, Luna-Vital, and González de Mejía (2017) characterized peptides from Brazilian Carioca and Mexican Black beans using digestive enzymes. Several peptides were derived but four of them had outstanding α-glucosidase and DPP-IV inhibition potentials. Peptides characterized were CPGNK, KTYGL, GGGLHK and KKSSG with DPP-IV inhibition IC_{50} values of 0.87 ± 0.02, 0.03 ± 0.00, 0.61 ± 0.10 and 0.64 ± 0.16 mg dry weight/ml respectively. α-glucosidase percentage inhibition shown by peptides were 37.60 ± 6.80 36.30 ± 8.80, 46.10 ± 8.30 and 49.34 ± 6.50 per mg dry weight respectively.

Mojica, Luna-Vital, and Gonzalez de Mejia (2018) evaluated the hypoglycemic potential of a hydrolyzed protein hydrolysate from black beans and peptides purified from it using *in vivo* and *in silico* analysis, they found that black bean fractions are functional in significantly reducing blood sugars by blocking glucose transporters. Rocha et al. (s2015) conducted a research to study the effect of germination and alcalase hydrolysis on the antidiabetic potential of peptides isolated from black bean proteins. Their results showed that neither the DPP-IV inhibition nor insulin secretion by pancreatic *β*-cells was improved, however, germination after a 24 h period was found to increase the α-amylase inhibition potential. Furthermore, they simulated the gastrointestinal digestion of common beans protein without any treatment and found that the peptides isolated were effective in inhibition thus improving the *in vitro* insulin secretion. The combination of 48 h germination with 1 h alcalase treatment in the course of their study led to the isolation of the trideca peptide RGPLVNPDPKPFL (1448.81 Da) of special interest due to its origin from phaseolin: the most abundant storage protein in beans accounting for about 40-50% of the total protein content (Montoya et al. 2010). This peptide, through *in silico* analysis was found to have possible DPP-IV inhibition potential.

Oseguera-Toledo, de Mejia, and Amaya (2015) conducted a study for *in vitro* evaluation and comparison of the antidiabetic potential of peptides derived from common beans which had undergone the hard-to-cook change due to high temperature and high humidity storage. The antidiabetic potential was measured on the basis of the effects of the isolated peptides on α-amylase, α-glucosidase and DPP-IV inhibition. Peptides of antidiabetic interest isolated in their study include LLSV (445 Da), WVVL (515 Da), and ALVLL (527 Da) originating from arcelain, vignain and arcelain-4 parental proteins respectively. Using the same protein sources, Oseguera-Toledo et al. (2016) determined the antidiabetic potentials of isolated peptides on the basis of their effects on insulin secretion, glucose uptake from insulin resistant adipocytes and DPP-IV inhibition. Their results showed that peptides with <1 kDa molecular weights increased the overall insulin secretion and glucose uptake on the diabetic rats. They include; FFL (425 Da), QLGGH (510.25Da), LLSL (444.29Da), QQEG (460.19Da), WGVFN (621.29Da), EPHGK (566.23Da), HVQNQ (624.29Da) and NDEPASG (688.26Da). Furthermore, the peptides and their bioactive sequences were discovered to inhibit the activities of DPP-IV proteins.

Mojica and de Mejia (2016) conducted a study on the optimized enzymatic synthesis of bioactive peptides from

Table 5. Leguminous sources of antidiabetic peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification /fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight (Da)	Antidiabetic mechanism	Reference
Black beans	Enzymatic	Alcalase	Ultrafiltration	AKSPLF ATNPLF FEELN LSVSVL	661.37 661.34 650.29 616.37	Reduced glucose uptake, blockage of glucose transport and DPP-IV inhibition *in vitro* and *in silico*	Mojica, Luna-Vital, and Gonzalez de Mejia 2018
Common beans	Enzymatic, germination and SGID	Alcalase from *Bacillus licheniformis*, pepsin and pancreatin		RGPLVNPDPKPFL	1448.81	DPP-IV inhibition *in vitro*	Rocha et al. 2015
Hard-to-cook beans	Enzymatic	Alcalase and bromelain	Ultrafiltration	LLSL WVVL ALVLL	445 515 527	Glucose uptake stimulation and DPP-IV inhibition *in vitro*	Oseguera-Toledo, de Mejia, and Amaya 2015
Common beans (Pinto Durgo and Black 8025)	Enzymatic, SGID	Alcalase, bromelain, pepsin, pancreatin	Ultrafiltration	FFL QLGGH LLSL QQEG WGVFN EPHGK HVQNQ NDEPASG	452.23 510.25 444.29 460.19 621.29 566.28 624.29 688.26	Insulin secretion, glucose uptake and DPP-IV inhibition *in vitro*	Oseguera-Toledo et al. 2016
Black beans (*Phaseolus vulgaris L.*)	Enzymatic	Trypsin, flavourzyme, proteinase k, thermolysin, alcalase, pepsin, papain, chymotrypsin	Dialysis	FEELN AKSPLF EGLELLLLLLAG	627.3 661.4 1252.8	α-amylase, α-glucosidase and DPP-IV inhibition *in vitro* and *in silico*	Mojica and de Mejia 2016
Soybeans (Aglycin peptide)	Chemical synthesis		HPLC	ASCNGVCSPFEMPP-CGSSACRCIPVGLVV-GYCRHPSG	3742.3	Blood glucose level reduction and enhancing insulin signal at gene levels *in vivo*	Lu et al. 2012
Meju, unsalted soybeans	Fermentation	*Bacillus subtilis* and *Aspergillus oryzae*	Peptides profile determined by Ultra performance liquid chromatography (UPLC)			Increased glucose tolerance and enhanced insulin sensitivity *in vivo*	Yang et al. 2012
Soybean condiment	Fermentation					α-amylase and α-glucosidase inhibition *in vivo* and *in vitro*.	Ademiluyi et al. 2014

black beans (*Phaseolus vulgaris* L.) and the evaluation of their antidiabetic potentials using *in silico* and biochemical analysis. Eight commercially available enzymes were used at different enzyme/substrate ratios (ESRs of 1:20, 1:30 and 1:50) and the generation of protein fractions occurred following 2, 3 and 4 h treatment. Their optimization results showed that the combination of a 2 h treatment with the alcalase enzyme (EC 3.4.21.62) and an ESR of 1:20 produced the best α-amylase, α-glucosidase and DPP-IV inhibition with inhibition values of 53.4, 66.1 and 96.7% respectively. *In silico* analysis showed that three FEELN, AKSPLF and EGLELLLLLLAG peptides inhibited DPP-IV more with free energy values of -9.5, -9.6 and -9.8kcal/mol respectively.

Soybeans

The history of Soybean dates back to the Asian continent where they serve as food and important economic commodity (Agyei, 2015). Soybeans has been long known and accepted as a functional protein source of high biological value that is readily available at low costs (Messina, 1999; Barac et al. 2004). Soybean contains twice as much protein (about 40%) than oil (about 20%) on dry basis (Nishinari et al. 2014). A larger fraction of its stored proteins are globulins which are ß-conglycinin (7S) and glycinin (11S). Though present in considerable amounts, soy proteins are of limited bioavailability due to certain antinutritional factors such as isoflavones, protease inhibitors, phytic acid, hemagglutinins and saponins (Miroljub et al. 2004).

Soybean is a functional food (Singh et al. 2008) possessing 'complete proteins' of high biological value and digestibility similar to that of casein, meat and egg (Singh et al. 2008; Hughes et al. 2011). Furthermore, it contains isoflavonoids which have similar activities with estrogen in that they exert agonistic or antagonistic effects on estrogen receptors (Bhathena and Velasquez, 2002). Estrogen has been reported to have antidiabetic effects by increasing insulin secretion, decreasing its resistance and increasing the pancreatic β-cell mass (Choi, Jang, and Park 2005).

Table 6. Fruits and leafy vegetable sources of antidiabetic hydrolysates and peptides.

Source	Extraction method(s)	Extraction tool	Separation/ purification /fractionation technique(s)	Hydrolysate name/ Peptide sequence	Molecular weight	Antidiabetic mechanism	Inhibition value	Reference
Juglans mandshurica Maxim. Fruit	Enzymatic	Alcalase	Ultrafiltration	<3 kDa fraction		α-glucosidase inhibition *in vitro* and *in vivo*	% inhibition (100mg/mL)	Wang, Li, and Lu 2018
				3–10 kDa fraction			46.6 ± 11.23	
				>10 kDa fraction			61.73 ± 1.93	
							<40.00	
Hemp (*Cannabis sativa* L.) seed protein	Enzymatic	Flavourzyme, protamex, neutrase, trypsin, papain and alcalase	Gel filtration chromatography and RP-HPLC	LR	287.2	α-glucosidase inhibition *in vitro*		Ren et al. 2016
				PLML	568.4			
Commercially Dried Laver (*Porphyra* Species) Seaweed	Enzymatic	Neutrase, pepsin, alcalase and trypsin	Ultrafiltration and gel chromatography	<5 kDa fraction		α-amylase inhibition *in vitro*	IC_{50} value (mg/mL)	Admassu et al. 2017
				5–10 kDa fraction			1.18	
				>10 kDa fraction			1.54	
				90-1000Da -FIII fraction			1.69	
							0.87	
Water melon seed	Enzymatic	Trypsin, pepsin and alcalase		Trypsin hydrolysate		α-amylase inhibition *in vitro*	IC_{50} value (mg/ml)	Arise, Yekeen, and Ekun 2016
							0.234	
				Pepsin hydrolysate			0.165	
				Alcalase hydrolysate			0.149	

Bioactive peptides can be isolated from soy via the action of enzymes (gastro intestinal or proteolytic of microbial origin) or microbial fermentation (Yang et al. 2012). These peptides have been found to possess antimicrobial, antidiabetic, antioxidant, anticancer, immunomodulatory and antihypertensive functionalities (Agyei, 2015).

Aglycin is a natural bioactive peptide isolated from soybean. It has a stable structure with three disulfide bonds surrounding six cysteine amino acids. It has an amino acid peptide sequence of ASCNGVCSPFEMPPCGSSACRCIP VGLVVGYCRHPSG with a molecular weight of 3742.3Da. In a research study conducted by Lu et al. (2012s, aglycin, was examined *in vivo* in diabetic mice regarding its antidiabetic potential. The mice were fed with a fat-rich diet, administered with streptozotocin intravenously to induce diabetes. Aglycin was dissolved in a 5 mg/mL saline solution and orally administered at a daily dosage of 50 mg/kg for a four-week period. It was found to increase glucose uptake, restore insulin signal transduction and regulate glucose homeostasis thereby significantly controlling hyperglycemia.

Fermentation of soy beans is an important unit operation carried out to improve its nutritional and functional properties. It involves the breakdown of macromolecules such as lipids, carbohydrates and proteins by enzymatic hydrolysis into micromolecules such as fatty acids, simple sugars, peptides and amino acids which improve the overall functional and sensory properties of the final product (Kwon et al. 2010). In a study conducted by Yang et al. (2012) the comparison of the antidiabetic potential of unfermented cooked soybeans and meju fermented by traditional and standardized methods was conducted on diabetic rats. Laboratory rats were fed with 15.1 ± 1.8 g/day for the TMS experimented rats and 14.1 ± 1.7g/day for MMS for 8 weeks. Their results showed that the fermented products in overall had better insulinotrpic potential through improved hepatic insulin sensitivity by the activation of insulin signaling and also by the stimulation of glucose-stimulated insulin. Ademiluyi et al. (2014s also investigated the antidiabetic effects of fermented soybean diet *in vivo* and *in vitro*. The *in vivo* results on streptozotocin (STZ)-induced diabetic rats exhibited a reversal in the blood glucose level to normal. The *in vitro* studies reflected an α-glucosidase and an α-amylase inhibition by the soybean extract.

Fruits and leafy vegetables

Fruits and leafy vegetables have relatively higher water content (61.0–94.7%) and low levels of protein (0.5-3.9%) and fat (trace – 0.4%) in comparison with other foods (Slavin and Lloyd, 2012). Examples of protein rich leafy vegetables and fruits include guava, bitter gourd, broccoli, spinach, and duckweed (Islam, Jalaluddin, and Hettiarachchy 2011; Rocha et al. 2015; Edelman and Colt, 2016). The proteins of most fruits are insufficient for proper functioning of the body and are usually concentrated in their seeds, resistant to digestive metabolism in the small intestine and bacterial breakdown in the large intestine (Southgate, 1991; Slavin and Lloyd, 2012). For these reasons, few research studies have been

conducted on the isolation of peptides and hydrolysates from fruits and leafy vegetables (Table 6).

Wang, Li, and Lu (2018) however, conducted a research study on the enzymatic isolation of antidiabetic peptides from hydrolyzed proteins of the walnut fruit - *Juglans mandshurica* Maxim. The protein isolates were further fractionated by ultrafiltration with 10 and 3KDa membranes respectively. The antidiabetic potentials of the hydrolyzed fractions were determined on the basis of their α-glucosidase inhibition *in vivo* using streptozotocin-induced diabetic mice. Experimental diabetic rats were grouped with one group administered a daily dosage of 800 mg/kg and the other 500 mg/kg. Their results showed that hydrolysate peptide fractions within the categories of lower (<3kDa) and medium (3–10 kDa) showed higher inhibition of the digestive enzyme with inhibition values of inhibition rates of 46.6 ± 11.23% and 61.73 ± 1.93% at concentration of 100 mg/mL. The higher weight fractions (>10 kDa) showed lower inhibition of 56.22 ± 1.55% at a concentration of 60 mg/mL. In addition, insulin secretion was found to increase at a rate of 23.71% and glycogen levels, liver glucokinase, and fasting blood glucose levels showed a decrease by 76.19, 69.54, 64.82% respectively.

Ren et al. 2016 in a research study identified and characterized two novel oligopeptides with α-glucosidase inhibition potentials from an unconventional plant source: the seed protein of hemp (*Cannabis sativa* L.). Subsequent to the defatting and dehydration of the hemp seed, the protein was extracted and hydrolyzed enzymatically with 6 proteases namely flavourzyme (EC 3.4.11.1), protamex (EC 3.4.21.14), neutrase, trypsin (EC 3.4.21.4), papain (EC 3.4.22.2) and alcalase (EC 3.4.21.62). The alcalase treatment showed the highest degree of hydrolysis and α-glucosidase inhibition and was further fractionated for the isolation of peptides. The dipeptide LR (287.2 Da) and the pentapeptide PLMLP (568.4 Da) were isolated.

Admassu et al. (2017s examined the α-amylase inhibition potential of protein hydrolysate from commercially dried laver (seaweed). In their study, the α-amylase inhibition of hydrolysates obtained from four different enzymatic treatments using neutrase, pepsin, alcalase and trypsin were examined. The pepsin hydrolysate was found to possess the strongest inhibition of 1.86 mg/mL as the evaluated IC_{50} value. Ultrafiltrative fractionation of this hydrolysate then followed in the order of <5 kDa, 5-10 kDa and >10 kDa fractions, among which the <5 kDa fraction showed the strongest α-amylase inhibition *in vitro*, with an IC_{50} value of 1.18mg/mL. Using gel chromatography, the <5 kDa fraction was further fractionated into three fractions classified as F-I to F-III and the F-III fraction found to possess the α-amylase strongest inhibition potential with IC_{50} value of 0.87mg/mL.

Arise, Yekeen and Ekuns (2016) isolated the protein in water melon seed and examined the α-amylase inhibition potential of its enzymatically digested hydrolysates, *in vitro*. The enzymes trypsin, pepsin and alcalase were used for hydrolysis and their hydrolysates were found to inhibit α-amylase with IC_{50} inhibition values of 0.234, 0.165 and 0.149 mg/ml respectively.

Nutraceutical properties of peptides and their bioavailablity

The desirable health activities of bioactive peptides make them suitable for recognition as nutraceuticals and functional foods though with fundamental bottlenecks such as health claims, consumer acceptance, production costs, product analysis and bioavailability (Li-Chan, 2015). Bioavailability of a peptide is its fraction that gets circulated and eventually actuated following its administration into the body. The relatively high molecular weights and hydrophilic characteristic of peptides with amino acid chain lengths greater than three reduces their intestinal and mucus permeation (Gleeson, Ryan, and Brayden 2016). Furthermore, their vulnerability to pancreatic digestive enzymes such as elastase, trypsin and chymotrypsin when orally administered is another issue of concern (Renukuntla et al. 2013). To annul these constraints and improve the bioavailability of orally administered peptides, the use of enzymatic inhibitors (such as serpin and aprotinin) absorption enhancers (such as thiolated polymers and chitosan), emulsions and microemulsions, microadhesive polymers, oral micro and nanoparticles and structural modification are employed (Ismail and Csóka, 2017) GLP-1 is a commercially available antidiabetic peptide drug with an amino acid sequence of *HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2*. Structural modification with biotin was used by Youn et al. (2008) for the successful modification of the peptide drug GLP-1. Their results showed that the oral administration of the modified drug improved its oral absorption and protected it against enzymatic breakdown, thus improving its bioavailability.

Other commercially available antidiabetic peptide drugs include Amylin (14-20)-NFLVHSS, Exendin-4(1-8)-HGEGTFTS-NH_2, (Pro^3)-Gastric Inhibitory Polypeptide -YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWK-HNITQ-NH_2 and C-Peptide (Acetate salt)-EAEDLQVGQVELGGGPGAGSLQPLALEGSLQ-NH_2, marketed by BACHEM biotech company, Switzerland.

Concluding remarks and future prospects

In recent decades, several therapies have emerged for the management of diabetes, among which the pharmaceutical remedy have been most prominent. Howbeit, several pharmacological agents have shown diverse metabolic alterations and side effects. Food derived hydrolysates and peptides however, have the precedence of causing minimal aftereffects. The abundance and natural availability of diverse plant and animal foods of high protein content adds to their preference as the suitable choice remedy for diabetes.

Presently, several BHs and BPs have been isolated from dairy, meat, cereals and legumes, nonetheless, more investigation should be done on their isolation from exceptional sources like fruits and leafy vegetables. Though

unconventional and with protein in petite quantities, BHs and BPs isolated from these sources can prove to be of extraordinary potential in the treatment of diabetes. Furthermore, there is need for more research with the purpose of concentrating and fortifying food-derived BHs and BPs to be as or even more effective than other pharmaceutical approaches while retaining their desired characteristic of minimal side effects.

Abbreviations

P	proline
L	leucine
C	cysteine
Q	glutamine
T	threonine
F	phenylalanine
V	valine
G	glycine
N	asparagine
H	histidine
E	glutamic acid
K	lysine
M	methionine
R	arginine
S	serine
D	aspartic acid
A	alanine
W	tryptophan
I	isoleucine
Y	tyrosine
IC_{50}	half maximal inhibitory concentration
PI	potency index
SGID	simulated gastrointestinal digestion
DPP-IV	Dipeptyl peptidase IV
RP-HPLC	reverse phase-high performance liquid chromatography
WPI	whey protein isolate
Da	Dalton

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