Food Chemistry: X 13 (2022) 100222

Contents lists available at ScienceDirect

Food Chemistry: X

journal homepage: www.sciencedirect.com/journal/food-chemistry-x

A comprehensive review on the glucoregulatory properties of food-derived bioactive peptides

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ARTICLE INFO

Keywords:
Bioactive peptides
Diabetes mellitus
Glucose homeostasis
Insulin resistance
Reproductive dysfunction

ABSTRACT

Diabetes mellitus, a group of metabolic disorders characterized by persistent hyperglycemia, affects millions of people worldwide and is on the rise. Dietary proteins, from a wide range of food sources, are rich in bioactive peptides with antidiabetic properties. Notable examples include AGFAGDDAPR, a black tea-derived peptide, VRIRLLQRFNKRS, a β-conglycinin-derived peptide, and milk-derived peptide VPP, which have shown antidiabetic effects in diabetic rodent models through variety of pathways including improving beta-cells function, suppression of alpha-cells proliferation, inhibiting food intake, increasing portal cholecystokinin concentration, enhancing insulin signaling and glucose uptake, and ameliorating adipose tissue inflammation. Despite the immense research on glucoregulatory properties of bioactive peptides, incorporation of these bioactive peptides in functional foods or nutraceuticals is widely limited due to the existence of several challenges in the field of peptide research and commercialization. Ongoing research in this field, however, is fundamental to pave the road for this purpose.

1. Introduction

Diabetes mellitus, a group of metabolic disorders characterized by persistent hyperglycemia, is a serious and long-term condition impacting the lives and well-being of people worldwide. The prevalence of adult diabetes is estimated to reach 578 million and 700 million by 2030 and 2045, respectively (Saeedi et al., 2019). There are two main forms of diabetes, type 1 diabetes or insulin-dependent diabetes mellitus and type 2 diabetes or the non-insulin-dependent diabetes mellitus. In type 1 diabetes, pancreatic β-cells fail to produce sufficient insulin due to a genetic disorder or an autoimmune response. Type 2 diabetes, which accounts for 90% of all diabetic patients, is an outcome of combined effect of insulin resistance and insufficient insulin secretion (Axelsson et al., 2017). Type 2 diabetes is closely related to obesity; the incidence and severity of diabetes is elevated in obese subjects. Uncontrolled hyperglycemia, the core problem in relation to type 2 diabetes and obesity, damages vascular system and increases the risk of cardiovascular disease, kidney injury, and retinal disease. It has been reported that type 2 diabetes is the leading cause of kidney failure and coronary artery diseases (Cecchini et al., 2010) while other complications of chronic diabetes include dementia, sexual dysfunction, depression, and lower-limb amputations (Trayhurn, 2013). Despite the presence of various medications for diabetes management, considerable research has been conducted towards finding effective naturally-derived compounds without side effects or toxicity (Park & Jang, 2017) as many glucose-lowering drugs are associate with side effects of severe hypoglycemia, idiosyncratic liver cell injury, lactic acidosis, permanent neurological deficit, digestive discomfort, headache, and dizziness (Cao & Liu, 2015; Neustadt & Pieczenik, 2008). Food-derived bioactive compounds may also be better tolerated by majority of patients in long

Abbreviations: Akt, Protein kinase B; AMPK, AMP-activated protein kinase; C/EBP-α, CCAAT/ enhancer binding protein alpha; CCK, Cholecystokinin; CCK-1R, CCK type 1 receptor; cGMP, cyclic guanosine-monophosphate; DPP-IV, Dipeptidyl peptidase IV; ERK1/2, Extracellular signal regulated kinase 1/2; GIP, Glucose-dependent insulinotropic polypeptide; GLP-1, Glucagon-like peptide 1; GLUT, Glucose transporter; IRS-1, Insulin receptor substrate-1; MAPK, Mitogen activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; PPARγ, Peroxisome proliferator associated receptor gamma; TZD, Thiazolidinedione.

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https://doi.org/10.1016/j.fochx.2022.100222
Received 1 September 2021; Received in revised form 3 January 2022; Accepted 18 January 2022
Available online 2 February 2022

term use.

Food proteins from different sources including animal and plant (Antony & Vijayan, 2021; Kehinde & Sharma, 2020) as well as edible insects (Lee et al., 2021) have been increasingly acknowledged for their potential benefits towards management of many chronic diseases including diabetes. The physiological properties of food proteins are carried out by bioactive peptides; the protein fragments encrypted within the parent protein with positive effects on body functions and/or human health beyond their nutritional value (Korhonen & Pihlanto, 2006). The physiological effects of bioactive peptides include antihypertensive, antioxidant, anti-inflammatory, antiatherogenic, opioid, antimicrobial, antithrombotic, immunomodulatory, and mineral binding properties (Chakrabarti, Jahandideh, & Wu, 2014; Erdmann, Cheung, & Schroder, 2008; Guha & Majumder, 2019; Nagaoka, 2019; Udenigwe & Aluko, 2012). These peptides can be released enzymatically, during food processing, or by microbial fermentation (Korhonen & Pihlanto, 2006; Wu, Jahandideh, Yu, & Majumder, 2015). Protein hydrolysates and bioactive peptides have also a great potential to regulate glucose metabolism (de Campos Zani, Wu, & Chan, 2018).

Here, we review the involvement of protein hydrolysates and bioactive peptides in the regulation of blood glucose and insulin sensitivity, categorize the food-derived bioactive peptides based on their mechanisms of action, and discuss the challenges and opportunities of the peptide discovery and research.

2. Antidiabetic potential of bioactive peptides

Effective diabetic management requires a comprehensive approach to reduce blood glucose, normalize β-cell functions, and improve insulin sensitivity through weight management, diet, or medication (Knowler et al., 2002; Van Gaal & Scheen, 2015). Dietary proteins have a great satiety effect coming from stimulating gut hormones secretion, increasing energy expenditure, and enhancing gluconeogenesis (Westerterp-Plantenga, 2008). Protein intake positively affects blood glucose, insulin secretion, and body fat (Layman et al., 2003). Although the beneficial effects of protein intake on energy homeostasis and glycemia management have been mainly attributed to amino acid composition (Westerterp-Plantenga, Lemmens, & Westerterp, 2012), the role of bioactive peptides as potential molecules accounting for these positive effects has been more recognized in recent years (Caron, Domenger, Dhulster, Ravallec, & Cudennec, 2017). The beneficial effects of milk protein-derived peptides on glycemia control have been well characterized (recently reviewed in (Horner, Drummond, & Brennan, 2016)). Diverse studies have also shown the protective effects of cereals (barley, oat, rice, and wheat), pseudocereals (amaranth, quinoa, and buckwheat), and legumes (soy, pea, and some types of beans) against diabetes. Administration of Alcalase oat protein hydrolysate (MW < 5 kDa; 1 g/kg BW) to streptozotocin (STZ)-induced diabetic mice reduced blood glucose through affecting food intake, insulin secretion and sensitivity, and glycogenesis (Wang et al., 2019; Zhang, Wang, Liu, & Sun, 2016). FLQPNLDEH, DLELQNNVFPH, and TPNAGVSGAAAGAGAGGKH were

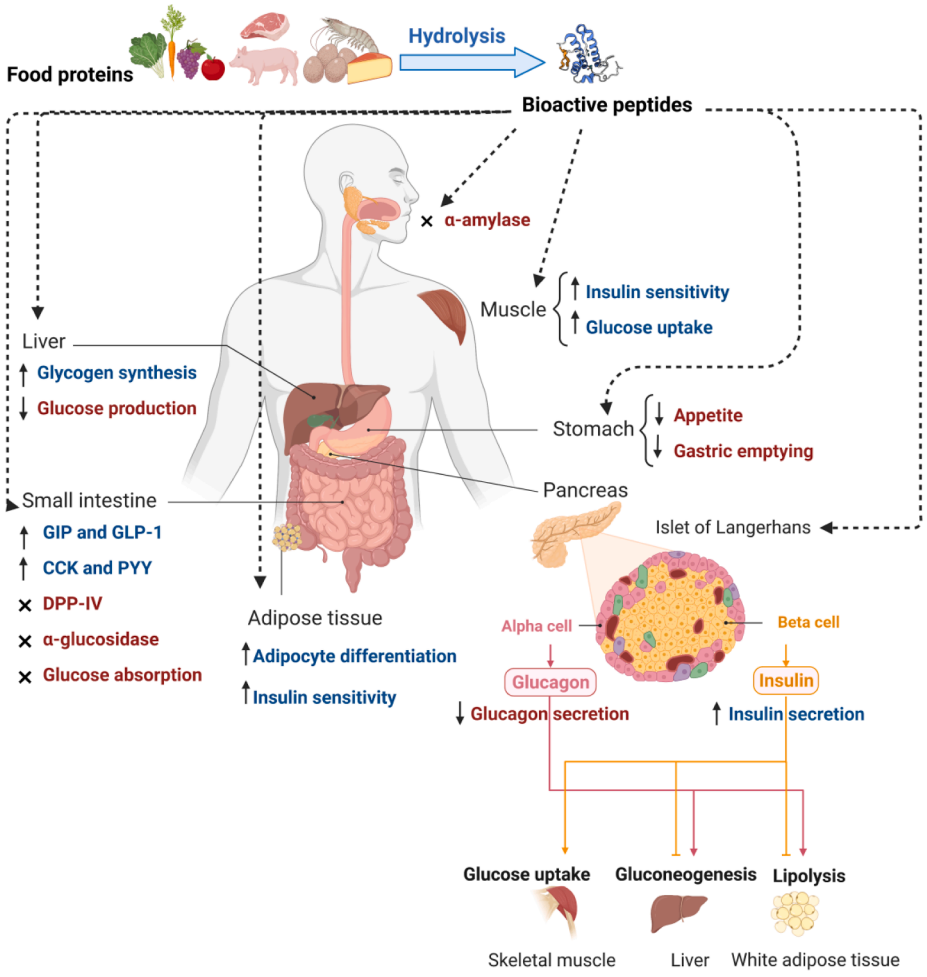

Fig. 1. Glucoregulatory mechanisms of bioactive peptides.

identified as the major peptides in oat protein hydrolysate (Zhang et al., 2016). Marine-derived bioactive peptides with glucoregulatory effects have also been commercialized and are available in the market. Nutripeptin™ a product containing cod hydrolysate has been marketed to improve glycemic index. Fortidium Liquamen® a white fish (*Molva molva*) autolysate containing fish oil and vegetable oil, is another example of commercialized food supplements with benefits on oxidative stress, glycemic index, psychological, and nervous balance (Guérard et al., 2010). Different mechanisms are involved in the glucoregulatory properties of bioactive peptides including carbohydrate digestion, gut hormone release, insulin secretion and function, glucose uptake, and adipose tissue modification (Fig. 1).

2.1. α-glucosidase and α-amylase inhibitors

The enzymes α-amylase and α-glucosidase are involved in the carbohydrate digestion; hydrolyzing complex carbohydrates into monosaccharides to be transported across the intestinal mucosa in the small intestine. While α-amylase breaks down long chain carbohydrates, α-glucosidase located in the brush border of the enterocytes lining the intestinal villi, facilitate the breakdown of disaccharides and oligosaccharides into absorbable monosaccharides. Inhibitors of α-amylase and α-glucosidase prolong the overall carbohydrate digestion time and reduce postprandial hyperglycaemia (Ross, Gulve, & Wang, 2004). Natural sources of α-glucosidase inhibitors are believed to lack the common side effects associated with synthetic α-glucosidase inhibitors including flatulence, abdominal cramping, vomiting, and diarrhea (Chaudhry et al., 2017). α-amylase and α-glucosidase inhibitory peptides have been identified from a variety of food sources, as reviewed elsewhere (Yan, Zhao, Yang, & Zhao, 2019), but notable examples include KLPGF from egg albumin with α-glucosidase inhibitory activity (IC_{50} values of 59.5 μM) and RCMAFLLSDGAAAAQQLLPQYW from cumin seeds with α-amylase inhibitory activity (IC_{50} values of 0.04 μM). Bioinformatic tools have been recently employed for the identification of bioactive peptides with antidiabetic properties. For example, five peptides with inhibitory activities against α-amylase were identified from pinto bean using a phage display technique to study protein-ligand interactions and receptor binding sites (Ngoh, Lim, & Gan, 2016). α-amylase inhibitory peptides were also identified from cumin (*Cuminum cyminum*) seed using an integrated bioinformatics-phage display approach (Siow, Lim, & Gan, 2017). This approach was shown to be very efficient in discovering peptides with α-amylase inhibitory properties; two novel α-amylase inhibitory peptides were identified from the 56 unknown peptides initially found in the cumin seed protein hydrolysate (Siow et al., 2017). Another bioinformatics-assisted approach involving PeptideRanker and Pepsite2 software was used to identify peptides with α-amylase inhibitory activity from pinto bean (Ngoh & Gan, 2018) as well as rambutan (*Nephelium lappaceum L.*) and pulasan (*Nephelium mutabile*) seed proteins (Evaristus, Wan Abdullah, & Gan, 2018). α-amylase inhibitory peptides have the capability to occupy the catalytic and substrate binding sites of the enzyme and prevent the α-amylase from binding or hydrolyzing the substrate (carbohydrate polymers). α-amylase inhibitory peptides may also attach to the starch and prevent it from digestion (Evaristus et al., 2018).

Bioactive peptides with α-glucosidase inhibitory properties have also been identified from milk (Konrad et al., 2014; Lacroix & Li-Chan, 2013), fish (Henriques et al., 2021), and egg proteins (Yu et al., 2011; Yu, Yin, Zhao, Liu, & Chen, 2012; Zambrowicz et al., 2015). Table 1 summarizes recent food-derived bioactive peptides with α-glucosidase and α-amylase inhibitory activities. Six weeks treatment of type 2 diabetic Goto-Kakizaki rats with PEP2DIA, a milk protein hydrolysate containing dipeptides with α-glucosidase inhibitory effect, has been reported to improve glycemic control in these rats (Boulier, Auger, & Romelard, 2021). Plant proteins are another source to produce α-glucosidase inhibitory peptides. Brewers' spent grain protein hydrolysates contain peptides with α-glucosidase as well as DPP-IV inhibitory activity (Connolly, Piggott, & FitzGerald, 2014). The proteolytic activity of the enzymes used for protein hydrolysis highly affects the bioactivity of peptides. Tryptic digests of the brewers' spent grain protein isolate showed the highest inhibition of α-glucosidase while Corolase PP hydrolysates exhibited the highest DPP-IV inhibitory potential. Alcalase and Prolyve 1000 hydrolysates on the other hand, exhibited the most potent angiotensin converting enzyme (ACE) inhibitory effects (Connolly et al., 2014). Walnut (*Juglans mandshurica Maxim.*) protein isolates prepared by alkali-soluble acid precipitation and separated into different molecular weight fractions; <3 kDa, 3–10 kDa, and > 10 kDa were tested for their α-glucosidase activity *in vitro*. The 3–10 k_D fraction exhibited α-glucosidase inhibitory rate of 61.7% and raised extracellular glucose consumption in insulin-resistant HepG2 cells. Administration of this peptide fraction to diabetic mice exhibited antidiabetic effects through reducing fasting blood glucose and increasing insulin secretion, liver glucokinase, and glycogen levels (Wang et al., 2018). Edible insect protein hydrolysates have also been recently reported to exert α-amylase and α-glucosidase inhibitory activities (Hall, Reddivari, & Liceaga, 2020; Yoon, Wong, Chae, & Auh, 2019). Alcalase-treated silkworm pupae and the Flavourzyme and Alcalase mixture-treated mealworm larvae were shown to inhibit α-glucosidase activity *in vitro* (Yoon et al., 2019). The cationic peptide fraction of cricket protein hydrolysate has been recently reported to exert α-amylase and α-glucosidase inhibitory activities with IC_{50} values of 18.5 and 13.9 μg/mL, respectively (Hall et al., 2020). The inhibitory mechanism of α-glucosidase inhibitors has been attributed to the hydrophobic interactions of these compounds with the active site of the enzyme (Bharatham, Bharatham, Park, & Lee, 2008). In summary, peptides with α-amylase and/or α-glucosidase inhibitory effects have been identified from various food proteins which can potentially mitigate postprandial hyperglycemia. The effectiveness of such peptides on improving blood glucose levels need to be further evaluated in animal models as well as diabetic patients.

2.2. Peptides inhibiting glucose absorption

The products of carbohydrate digestion, namely glucose and galactose, are transported across the enterocytes through the intestinal brush-border membrane. This process occurs in two stages involving active sodium-glucose cotransporter 1 (SGLT1) and facilitative glucose transporter 2 (GLUT2). Thirty minutes after food consumption, the products of digestion reach the apical membrane of the jejunum where their absorption into the epithelial cells occurs predominantly by the SGLT1. GLUT2, on the other hand, is considered to provide basolateral exit of these hexoses from epithelial cells into the circulation (Chen, Tuo, & Dong, 2016; Roder et al., 2014). Therefore, factors influencing SGLT1 and GLUT2 activities will also alter glucose absorption and metabolism. SGLT1 is also shown to play an important role in intestinal glucose sensing and incretin secretion (Roder et al., 2014). Food-derived peptides targeting transporters involved in glucose absorption are less explored. Alcalase hydrolysate of black bean protein reduced postprandial glucose in an oral glucose tolerance test in normal healthy rats (Mojica, Gonzalez de Mejia, Granados-Silvestre, & Menjivar, 2017). This protein hydrolysate further reduced fasting glucose in hyperglycemic rats receiving two intraperitoneal injections of streptozotocin (Mojica et al., 2017). Oral administration of rice albumin to healthy rats has been reported to suppress blood glucose elevation in response to both starch and glucose loading (Ina et al., 2016). Tryptic digests of rice albumin containing indigestible high molecular weight (14 kDa) and low molecular weight (2 kDa) fractions, also suppress postprandial blood glucose elevation in healthy rats by inhibiting glucose uptake into small intestinal epithelial cells (Ina et al., 2020). The inhibitory mechanisms of these fractions were different; the high molecular weight fraction worked like dietary fibers by adsorbing glucose and retarding its diffusion rate while the low molecular weight fraction inhibited the expression of SGLT1 (Ina et al., 2020).

Table 1
Some examples of food-derived bioactive peptides with antidiabetic properties (α-amylase, α-glucosidase, and DPP-IV inhibition).

Source	Treatments	Identified peptides	Mechanism of action	Model	Reference
Sardine muscle	Subtilisin, trypsin, flavourzyme	Peptides < 1400 Dalton, NAPNPR, YACSVR	DPP-IV inhibition	*In vitro*	Rivero-Pino et al. (2020)
Sardine muscle	Alkaline protease	VW, YYPL	α-glucosidase inhibition	*In vitro*	Matsui, Oki, & Osajima (1999)
Antarctic krill protein	Corolase PP	KVEPLP, PAL	DPP-IV inhibition	*In vitro*	Ji, Zhang, & Ji (2017)
Salmon gelatin	Corolase PP	GGPAGPAV, GPVA, PP, GF, arginine, tyrosine	DPP-IV inhibition, antioxidant	*In vitro*	Neves et al. (2017)
Casein (derived from bovine and camel milk)	Alcalase, pronase, and simulated gastrointestinal digestion	FLWPEYGAL, ACGP, DGALHPPL LPTGWLM, MFE, GPAHCLL HLPGRG, QNVLPLH, PLMLP	α-amylase inhibition α-glucosidase inhibition DPP-IV inhibition	*In vitro*	Mudgil et al. (2021)
Camel whey proteins	Pepsin	PAGNFLMNGLMHR, PAVACCLPPLPCHM, MLPLMLPFTMGY, PAGNFLPPVAAAPVM, CCGM, MFE, FCCLGPVPP	α-amylase and α-glucosidase inhibition	*In vitro* and *in-silico*	Baba et al. (2021)
Egg yolk protein (defatted)	Pepsin	YIEAVNKVSPRAGQF, YINQMPQKSRE, YINQMPQKSREA, VTGRFAGHPAAQ	DPP-IV inhibition, antioxidant activity	*In vitro*	Zambrowicz et al. (2015)
Egg white proteins	Alcalase	RVPSLM, TPSPR	α-glucosidase inhibition	*In vitro*	Yu et al. (2011)
Brewers' spent grain protein-enriched isolate	Alcalase and simulated gastrointestinal digestion	ILDL, ILLPGAQDGL	DPP-IV inhibition	*In vitro*	Connolly et al. (2017)
Chickpea Protein	Pepsin and pancreatin Bromalin	PHPATSGGGL, YVDGSGTPLT, SPQSPPFATPLW, YVDGSGTPLT GKAAPGSGGGTKA, KMTAGSGVT, GLTQGASLAGSGAPSPLF	DPP-IV, α-amylase, and α-glucosidase inhibition	*In vitro*	Chandrasekaran, Luna-Vital, and de Mejia (2020)
Kiwicha protein	Pepsin and pancreatin	FLISCLL, SVFDEELS, DFIILE, NRPET, HVIKPPS	α-amylase and DPP-IV inhibition	*In vitro*	Vilcacundo, Martinez-Villaluenga, Miralles, and Hernandez-Ledesma (2019)
Common bean	Germination, alcalase hydrolysis, and simulated gastrointestinal digestion	RGPLVNPDPKPFL	α-amylase and DPP-IV inhibition	*In vitro*	de Souza Rocha et al. (2015)
Pigeon pea protein	Thermoase	Peptide fractions of < 1, 1–3, 3–5, 5–10, >10 kDa	α-amylase and α-glucosidase inhibition, antioxidant	*In vitro*	Olagunju, Omoba, Enujiugha, Alashi, and Aluko (2021)
Quinoa protein (11S seed storage globulin B)	Simulated gastrointestinal digestion	IQAEGGLT, DKDYPK, GEHGSDGNV	DPP-IV, α-amylase, and α-glucosidase inhibition	*In vitro*	Vilcacundo, Martínez-Villalueng, and Hernández-Ledesma (2017)
Cummin seeds	Protamex	FFRSKLLSDGAAAAKGALLPQYW, RCMAFLLSDGAAAAQQLLPQYW, DPAQPNYPWTAVLVFRH	α-amylase inhibition	*In vitro*	Siow and Gan (2016)
Soy protein	Alkaline proteinase	LLPLPVLK, SWLRL, WLRL	α-glucosidase inhibition	*In vitro*	Wang et al. (2019)
Silk worm pupae proein	*In-silico* digestion and screening	SQSPA, QPGR, QPPT, NSPR	α-glucosidase inhibition	Quantitative structure–activity relationship modeling	Zhang et al. (2016)
Cricket protein	Alcalase and simulated gastrointestinal digestion (pepsin, bile salts and pancreatin) of the supernatant	Twenty eight peptides were identified but none of the peptides were verified agaist α-amylase and α-glucosidase enzymes	α-amylase and α-glucosidase inhibition	*In vitro*	Hall et al. (2020)
Mealworm larvae, cricket and silkworm pupae proteins	Flavourzyme and alcalase	Not determined	α-glucosidase inhibition	*In vitro*	Yoon et al. (2019)
Lesser mealworm protein	Thermolysin	Not determined	DPP-IV inhibition	*In vitro*	Lacroix, Davalos Teran, Fogliano, and Wichers (2019)
Cricket	Alcalase and simulated gastrointestinal digestion (pepsin, bile salts, and pancreatin)	Not determined	DPP-IV inhibition	*In vitro*	Hall, Johnson, and Liceaga (2018)
Housefly larvae	Water extraction	Protein fractions of > 6KDa molecular weight	DPP-IV inhibition	*In vitro*	Li et al. (2017)

2.3. Insulinotropic peptides

The impairment of glucose-stimulated insulin secretion is a hallmark of β-cell failure in type 2 diabetes. β-cells are involved in insulin secretion by continually monitoring and responding to dietary nutrients to best meet the needs of the organism. While glucose is the primary stimulus for insulin secretion, specific amino acids such as Arg and Glu and fatty acids also regulate insulin secretion (Newsholme & Krause, 2012). The mixed nutrient sensing and outputs of glucose, amino acid, and fatty acid metabolism generate the metabolic coupling factors which activate signals to promote insulin biosynthesis as well as the movement of insulin containing vesicles to the cell surface and insulin release (Newsholme & Krause, 2012). Primary metabolic coupling factors in β-cells include ATP, NADPH, glutamate, long chain acyl coenzyme A, and diacylglycerol. Failure to generate enough coupling factors in a coordinated manner may underlie the failure of β-cell to secrete insulin during the pathogenesis of type 2 diabetes (Newsholme & Krause, 2012). Mitochondria play a key role in insulin secretion by generating ATP and other coupling factors. A rise in the ATP/ADP ratio and suppression of the ATP-sensitive potassium (K_{ATP}) channels activates the voltage-gated Ca^{2+} channels, which eventually lead to stimulation of insulin granule exocytosis (Jensen et al., 2008). Insulinotropic properties of food proteins have long been known (Calbet & MacLean, 2002; Floyd, Fajans, Conn, Knopf, & Rull, 1966; Lang et al., 1999; van Loon et al., 2003). The generation of certain peptides during protein digestion as well as composition and concentration of released amino acids are important factors in stimulating insulin secretion (Schmid et al., 1992). L-arginine is one such amino acid with strong insulin secretagogue properties. This amino acid also has a synergic effect for nutrient-dependent insulin secretion (Krause et al., 2011). In addition to the acute effects on β-cells and insulin secretion, amino acids may impact on insulin secretion and cellular integrity by influencing gene expression in β-cells following chronic exposure (Newsholme & Krause, 2012). Branched-chain amino acids and hydrophilic peptides have been reported to exert insulinotropic properties (Nongonierma et al., 2013). Similarly, Leu, Ile, Val, Lys, and Thr, generated after whey protein ingestion, were shown to have the strongest correlation with insulin response in healthy subjects (Nilsson, Stenberg, Frid, Holst, & Bjorck, 2004). The enzymatic hydrolysis of whey proteins has been reported to enhance insulin secretion in pancreatic BRIN-BD11 β-cells, improve blood glucose clearance, and restore the glucose-induced pancreatic islet capacity to secrete insulin in ob/ob mice (Gaudel et al., 2013). Fermented soybean, from which *Meju*—the Korean product used in many foods, also affects glucose homeostasis (Kwon, Hong, Lee, Sung, & Park, 2007; Yang, Kwon, Kim, Kang, & Park, 2012). Kwon and coworkers found that both isoflavonoid and peptide fractions of fermented *meju* affected adipocyte differentiation and insulin secretion (Kwon et al., 2011). Water extracts of 60-day fermented *meju*, mostly containing peptides of 15 KDa molecular weight, promoted insulin-stimulated glucose uptake and adipocyte differentiation in 3T3-L1 adipocytes. This fraction also enhanced glucose-stimulated insulin secretion and moderately enhanced β-cell proliferation in Min6 insulinoma cells. The specific sequence of peptides, however, was not identified in this fraction (Kwon et al., 2011).

2.4. Incretin mimetic peptides

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released by the intestinal K and L cells, respectively, after meal ingestion are known as incretins (Pais, Gribble, & Reimann, 2016). These peptidic hormones regulate postprandial insulin secretion (Drucker & Nauck, 2006). Destruction of pancreatic islets in diabetic patients results in the reduced effect of incretins (Nauck, 2011). Administration of incretins to diabetic patients has been reported to increase β-cell proliferation along with insulinotropic effects without the risk of hypoglycaemia (Nauck & Meier, 2010). Enhancement of endogenous GLP-1 secretion by dietary factors is a promising strategy for the prevention of hyperglycemia in type 2 diabetes. Amino acids, particularly glutamine, stimulate GLP-1 secretion and increase plasma GLP-1 level in humans (Greenfield et al., 2009; Samocha-Bonet et al., 2011). Wheat protein hydrolyzed by bacterial protease contains a glutamine rich low molecular weight fraction which increases GLP-1 secretion through activation of the Ca^{2+}/calmodulin-dependent kinase II pathway in GLUTag cells (enteroendocrine L cell line) (Kato, Nakanishi, Tani, & Tsuda, 2017). The effectiveness of this treatment on incretin secretion and regulation of blood glucose was further confirmed in normal healthy Sprague Dawley rats (Kato et al., 2017). Oligopeptides including LGG and GF along with the non-metabolizable peptide transporter-1 (PEPT1) substrate glycine-sarcosine, have been reported to enhance GLP-1 release in murine primary L cells. Mechanistic experiments revealed that PEPT1 and activation of Ca^{2+} channels are involved in the glycine-sarcosine-stimulated GLP-1 secretion (Diakogiannaki et al., 2013). The ileal administration of zein hydrolysate (prepared by papain) enhanced GLP-1 secretion while attenuated the glucose-induced hyperglycemia by enhancing insulin secretion in normal healthy rats (Mochida, Hira, & Hara, 2010). In a follow-up study, the anti-hyperglycemic effect of this treatment was shown in normal and diabetic rats. The oral administration of the zein hydrolysate attenuated hyperglycemia by stimulating GLP-1 and GIP secretion in normal rats. The involvement of increased GLP-1/GIP secretion was determined using GLP-1/GIP receptor antagonists. This treatment also effectively reduced the glycemic response under oral glucose tolerance test in diabetic rats which was accompanied by increased GLP-1 and insulin secretion (Higuchi, Hira, Yamada, & Hara, 2013).

2.5. DPP-IV inhibitors

Incretins are rapidly cleaved and inactivated after release into the circulation by the action of the serine protease dipeptidyl peptidase IV (DPP-IV) (Irwin & Flatt, 2013). DPP-IV inhibitors are a class of oral antidiabetic drugs which can extend the half-life of the endogenous GLP-1 and GIP, and in turn prolong the insulin response (Green, Flatt, & Bailey, 2006). The potential of proteins from nine different food commodities as the precursors of DPP-IV inhibitory peptides was evaluated through an in-silico approach (Lacroix & Li.-Chan, 2012). Milk caseins and bovine meat and salmon collagens were reported to be the best sources to produce DPP-IV inhibitors, whereas oat proteins were the least promising sources. Among the 2256 fragments from 34 proteins with peptide sequences matching the reported DPP-IV inhibitory peptides in the literature, dipeptides GA, GP, and PG were the most frequently occurring sequences (Lacroix & Li.-Chan, 2012). IPI has been reported as the most potent DPP-IV inhibitory peptide with the IC_{50} of 5 μM, which is present in the primary sequence of several food proteins (Nongonierma & FitzGerald, 2014). Bioactive peptides with DPP-IV inhibitory effect have been reported to contain proline especially on the second *N*-terminus and flanked by leucine, valine, or phenylalanine (Harnedy-Rothwell et al., 2020; Rivero-Pino, Espejo-Carpio, & Guadix, 2020). Bovine α-lactalbumin hydrolysates generated by alcalase contain DPP-IV inhibitory peptides, ELKDLKGY and ILDKVGINY. These peptides could form hydrogen bonds, pi-cation interactions, and salt bridges with DPP-IV enzyme as shown by molecular docking studies (Gao, Gong, & Mao, 2020). Camel milk also contains peptides with DPP-IV inhibitory effects, as well as positive effects on insulin receptor activation and glucose uptake (Ashraf et al., 2021). Subjection of the alcalase hydrolysates of the brewers' spent grain protein to the simulated gastrointestinal digestion improved DPP-IV inhibitory activity and two novel DPP-IV inhibitory peptides of ILDL and ILLPGAQDGL were identified (Connolly, O'Keeffe, Nongonierma, Piggott, & FitzGerald, 2017). Although food proteins have been suggested to be precursors for DPP-IV inhibitory peptides (Liu, Cheng, & Wu, 2019), most of the studies in this area have been performed through *in-silico* or *in vitro* assays using biochemical tools involving purified porcine or human DPP-IV enzymes

and a standard substrate for bioactivity measurements (Lammi et al., 2018). Despite being advantageous, these methods provide insufficient characterization of the peptides' activity before performing expensive *in vivo* studies. Potential degradation of peptides by membrane associated peptidases can affect bioactive peptides' activity which is not considered in *in vitro* assays. IPVDM is a boarfish-derived peptide with DPP-IV inhibitory activity. While the IC_{50} value of 21.7 μM has been reported for the *in vitro* assay, the IC_{50} value of this peptide for the cell-based assay is 44.3 μM. Similarly, GPSI, was shown to exert significantly lower activity in the cell-based assay (>312.5 μM) when compared to the *in vitro* assay (72.8 μM) (Harnedy-Rothwell et al., 2020). To fill the gap between the biochemical assays and *in vivo* studies, Lammi and co-workers have recently developed fast and sensitive DPP-IV assays using human intestinal cells and human serum. These assays were further validated on previously identified soy (IAVPTGVA) and lupin (LTFPGSAED) peptides with known DPP-IV inhibitory activity (Lammi et al., 2018) This experimental approach which combines *in-situ* and *ex vivo* DPP-IV assays seems to be promising for identifying food-derived peptides with DPP-IV inhibitory effect in a more realistic fashion compared to the *in vitro* biochemical assays. Only a few studies have explored the physiological effects of DPP-IV inhibitory peptides *in vivo*. The antidiabetic potential of Atlantic salmon skin gelatin hydrolysate with *in vitro* DPP-IV inhibitory activity has been assessed in streptozotocin-induced diabetic rats (Hsieh, Wang, Hung, Chen, & Hsu, 2015). The 5-week oral administration of this treatment at a single dose of 300 mg/day in diabetic rats reduced blood glucose levels during an oral glucose tolerance test, inhibited plasma DPP-IV activity, and increased plasma GLP-1 and insulin levels (Hsieh et al., 2015). Tilapia skin gelatin hydrolysate has also been shown to improve glucose tolerance and increase GLP-1 and insulin secretion in streptozotocin-induced diabetic rats (Wang et al., 2015). LPQNIPPL is a gouda cheese-derived octapeptide with a high DPP-IV inhibitory activity. Administration of this peptide to female rats improved blood glucose response after an oral glucose tolerance test. However, plasma DPP-IV activity or concentration of incretin hormones were not reported (Uenishi, Kabuki, Seto, Serizawa, & Nakajima, 2012), which makes it difficult to understand the mechanisms underlying these effects *in vivo*. Ileal administration of a zein hydrolysate attenuated the hyperglycemia in normal healthy Sprague Dawley rats by enhancing active GLP-1 concentration, insulin secretion, and reducing plasma DPP-IV activity (Mochida et al., 2010). A low molecular weight fraction (<1 kDa) of a Flavourzyme porcine skin gelatin hydrolysate shows *in vitro* DPP-IV inhibitory activity. The daily administration of this fraction to streptozotocin-induced diabetic rats at the dose of 300 mg/day improved glucose tolerance, reduced plasma DPP-IV activity, increased GLP-1 and insulin levels, and reduced glucagon content in these rats. GPFPLPD, GGKPSSMT, and GGHLFFC were the peptides identified from porcine skin gelatin hydrolysate (Huang, Hung, Jao, Tung, & Hsu, 2014). AGFAGDDAPR is a Chinese black tea-derived peptide with *in vitro* DPP-IV inhibitory properties. Administration of this peptide (400 mg/day) to streptozotocin-induced diabetic mice for 57 days enhanced blood GLP-1 and insulin concentration, improved beta-cells function, and suppressed proliferation of alpha-cells compared to the diabetic control mice (Lu et al., 2019). Therefore, DPP-IV inhibitory peptides have a great potential for glycemic control through enhancing GLP-1 and insulin secretion.

2.6. Satietogenic peptides

Altered satiety signaling is involved in the development of obesity and type 2 diabetes (Hellstrom, 2013). Various gut hormones including incretins have important physiological roles in the regulation of hunger and satiety. A decrease in the concentrations of ghrelin, the orexigenic gut hormone, along with an increase in anorexigenic peptides such as cholecystokinin (CCK), peptide YY (PYY), and GLP-1 are immediate changes that occur postprandially. Acting in concert on the brain, these hormones induce an eventual decrease in hunger and increase in satiety leading to meal termination (Field, Chaudhri, & Bloom, 2010). Pharmacological interventions enhancing the gut hormone signaling are considered potential treatments for obesity and type 2 diabetes.

Dietary proteins are believed to induce satiety feeling potentially through increasing the concentration of satiety hormones and energy expenditure (Veldhorst et al., 2008). Amino acid composition of ingested proteins has also been suggested to play a major role in the satiety-induced effects of high-protein diets (Mellinkoff, Frankland, Boyle, & Greipel, 1956). CCK is released from I cells of the small intestine in response to fat and protein and stimulates CCK1 receptors on vagal afferents in the brainstem and hypothalamus (Blevins, Stanley, & Reidelberger, 2000). Food proteins contain peptides with stimulating effects on CCK secretion. The potential of chicken, pork, beef, beef liver, and egg white protein hydrolysates on CCK release from STC-1 cells was examined in one study (Sufian et al., 2006). Chicken and pork pepsin hydrolysates were shown to bind to the rat small intestinal brush border membrane and release CCK from STC-1 cells in a dose-dependent manner (Sufian et al., 2006). Orogastric administration of these protein hydrolysates to normal healthy rats suppressed 60-min food intake only in the porcine meat hydrolysate group (Sufian et al., 2006).

Marine-derived proteins and bioactive peptides also have strong satiety effects. Blue whiting (*Micromesistius poutassou*) muscle hydrolysate consisting of short peptides in range of 1000 Da enhanced CCK secretion in STC-1 cell line (Cudennec, Ravallec-Ple, Courois, & Fouchereau-Peron, 2008). The administration of blue whiting hydrolysate to rats (normal healthy) reduced the short-term food intake along with an increase in the CCK and GLP-1 plasma levels. Chronic administration of this marine hydrolysate also decreased body weight gain in these rats (Cudennec, Fouchereau-Peron, Ferry, Duclos, & Ravallec, 2012). Administration of a protein hydrolysate from smooth hound (*Mustelus mustelus*) to Wistar rats (normal healthy) for 21 days reduced the body weight compared to the control group (Bougatef et al., 2010). Despite the reduction in body weight, no significant changes in plasma CCK levels after thirty minutes of the oral administration of this hydrolysate was observed (Bougatef et al., 2010). Legume proteins from different sources such as soy (Nakajima, Hira, Eto, Asano, & Hara, 2010; Nishi, Hara, & Tomita, 2003; Nishi, Hara, Asano, & Tomita, 2003; Sufian et al., 2011), and some under-utilized beans such as Country bean and Yard long bean (Sufian, Hira, Asano, & Hara, 2007) are other potential candidates with beneficial effects on gut hormone release and appetite control. Jang and co-workers reported the anti-obesity effects of an isoflavone-free peptide mixture derived from black soybean (*Rhynchosia volubilis*) in high fat diet-fed mice (Jang et al., 2008). This treatment reduced food intake through activation of the leptin-like signaling in hypothalamus and reduced body weight gain in mice fed a high fat diet for 13 weeks. Interestingly, identification of a hepta peptide IPPGVPY in the plasma 30 min after oral administration of 1 g black soybean peptide mixture suggests the potential role of absorbed peptides in the observed physiological effects *in vivo* (Jang et al., 2008). Intraduodenal infusion of pepsin hydrolyzed soybean β-conglycinin suppressed food intake in normal healthy rats. The suppression of food intake by β-conglycinin hydrolysate was abolished by an intravenous injection of a selective peripheral CCK receptor antagonist. The infusion of β-conglycinin hydrolysate into the rat duodenum strongly suppressed gastric emptying with marked increase in portal CCK level. Further experiments revealed that β-conglycinin hydrolysate binds to components of the rat intestinal cell membrane directly and stimulates CCK release from these cells (Nishi et al., 2003). Arg residue in protein structures has been reported to play a role in CCK release (Nishi, Hara, Hira, & Tomita, 2001). The fragment from 51 to 63 of the β-conglycinin's β-subunit with the sequence of VRIRLLQRFNKRS had the strongest binding activity to the rat small intestinal mucosal cells. Intraduodenal infusion of this peptide to normal healthy rats inhibited food intake and markedly increased portal CCK concentration. Different model peptides with Arg and Gly residues were constructed to further explore the structure requirements for the observed effects among which only GRGRGRG had strong

binding affinity (Nishi, Hara, Asano, et al., 2003). Although food-derived peptides with CCK release stimulation are capable of controlling appetite, it should be noted that CCK release per se is not efficient in reducing long-term food intake and weight loss (Hellstrom, 2013).

2.7. Peptides improving peripheral glucose uptake

2.7.1. Activating phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway

Insulin triggers signaling events that control the metabolic fate of nutrients. The phosphatidylinositol 3-kinase (PI3K) and the mitogen activated protein kinase (MAPK) pathways are the major signaling cascades mediating most metabolic and transcriptional effects of insulin (Laviola et al., 2006). The MAPK pathway mainly controls the mitogenic, growth, and cell differentiation processes in cells; phosphorylation and activation of Extracellular signal regulated kinase 1/2 (ERK1/2) in this pathway plays a direct role in cell proliferation and differentiation (Boucher, Kleinridders, & Kahn, 2014; Laviola et al., 2006). The PI3K pathway, being the other major signaling cascade of insulin, is responsible for most metabolic effects of insulin. Activation of the protein kinase B (Akt) in this pathway leads to the translocation of glucose transporters from intracellular sites to the plasma membrane for glucose uptake. Glucose transporters facilitate the transport of glucose passively across the cell membrane. Glucose transporter 4 (GLUT4) is the main isoform which mediates glucose uptake into muscle and fat cells (Bilous & Donnelly, 2010). Peripheral glucose uptake is impaired in insulin resistance and type 2 diabetes (Goodpaster et al., 2014). Indeed, the disruption of intracellular signaling pathways involved in GLUT4 translocation leads to insufficient channels for glucose uptake and accumulation of glucose extracellularly in insulin resistance and type 2 diabetes (Shulman, 2000).

The potential benefits of amino acids and bioactive peptides on enhancing glucose uptake have been reported in literature. Leu and Ile are the two amino acids accelerating glucose uptake (Doi et al., 2005; Nishitani et al., 2002). Daily administration of aglycin, a 37-amino-acid polypeptide isolated from soybean, at dose of 50 mg/kg/day for 4 weeks, was reported to effectively control hyperglycemia and enhance oral glucose tolerance in streptozotocin/high-fat-diet-induced diabetic mice (Lu et al., 2012). While insulin signaling was perturbed in skeletal muscle in these diabetic mice, aglycin restored insulin signaling by maintaining insulin receptor and insulin receptor substrate 1 (IRS-1) expression at both mRNA and protein levels. This peptide further enhanced phosphorylation of IRS-1 and Akt and increased membrane GLUT4 protein expression thereby increasing glucose uptake in skeletal muscle (Lu et al., 2012). Agents that block the renin angiotensin system have shown glucoregulatory potential in the context of metabolic syndrome (Jahandideh & Wu, 2020). The work from our group has shown the insulin sensitizing and mimetic properties of different food-derived antihypertensive peptides (Chakrabarti, Jahandideh, Davidge, & Wu, 2018; Jahandideh et al., 2019; Jahandideh, Chakrabarti, Davidge, & Wu, 2017). VPP and IPP, the casein-derived tripeptides with well-known antihypertensive properties (Kim, Kim, & Choue, 2008; Nakamura et al., 2011) also enhanced insulin signaling and contributed toward the prevention of insulin resistance in the presence of tumor necrosis factor in 3T3-F442A adipocytes (Chakrabarti, Jahandideh, Liu, & Wu, 2018). Egg white hydrolysate prepared by thermolysin and pepsin with antihypertensive properties (Jahandideh et al., 2016) also enhanced insulin effects on the upregulation of protein kinase B/Akt phosphorylation as well as increased ERK1/2 phosphorylation to a level similar to that of insulin in 3T3-F442A adipocytes (Jahandideh et al., 2017). Administration of this protein hydrolysate to insulin resistant rats further increased insulin sensitivity, improved oral glucose tolerance, and reduced systemic inflammation. EWH exhibited its insulin sensitizing effects through potentiating insulin induced Akt phosphorylation in muscle and adipose tissue (de Campus Zani, Jahandideh, Wu, & Chan, 2019; Jahandideh et al., 2019).

2.7.2. Activating AMP-activated protein kinase (AMPK) pathway

AMP-activated protein kinase (AMPK) is an evolutionarily conserved serine/threonine kinase known as a master regulator of metabolism (Ruderman & Prentki, 2004). Activation of this nutrient-sensing kinase occurs when cellular energy levels are low and results in restoration of normal energy levels by stimulating processes that generate ATP (such as fatty acid oxidation) and inhibiting those that use ATP (like triglyceride and protein synthesis) (Ruderman, Carling, Prentki, & Cacicedo, 2013). While AMPK pathway is impaired in animals and humans with type 2 diabetes (Coughlan, Valentine, Ruderman, & Saha, 2014), activators of this pathway can improve insulin sensitivity by stimulating glucose uptake in skeletal muscle, enhancing fatty acid oxidation in adipose tissue, and reducing hepatic glucose production (Zhang, Zhou, & Li, 2009).

Protein hydrolysates and bioactive peptides have been reported to activate AMPK pathway. Black soybean peptides were shown to activate AMPK *in vitro* (in myotubes) and *in vivo* (Jang et al., 2008). These peptides also restored insulin signaling in normal and insulin resistant HepG2 cells by stimulating Akt serine phosphorylation, forkhead transcription factor, Foxo1, and glycogen synthase kinase-3β (Jang et al., 2010). Oral administration of black soybean peptides to diabetic (db/db) mice showed antidiabetic effects partially through suppression of hepatic endoplasmic reticulum stress (Jang et al., 2010). The black soy peptide supplementation has also been reported to have a modest effect on reducing fasting glucose and improving glucose tolerance in Korean adults with prediabetes (fasting glucose $\geq$ 110 mg/dL) in a double-blind randomized placebo-controlled trial (Kwak et al., 2010). The low molecular weight (300–500 Da) fractions of soybean peptides have been reported to improve glucose uptake in L6 muscle cells in the presence of insulin. These charged peptides also activated AMPK in muscle cells, however, no increase in glucose uptake was observed in the absence of insulin in these cells (Roblet et al., 2014). IAVPGEVA, IAVPTGVA, and LPYP, the peptides derived from soy glycinin hydrolysate, have been reported to activate AMPK pathway in hepatic cells. These peptides also increased glucose uptake in hepatic cells via activation of Akt (Lammi, Zanoni, Arnoldi, & Vistoli, 2015). Although this study demonstrates the potential of these peptides for enhanced glucose uptake via distinct Akt and AMPK pathways, the major effect of AMPK activation in hepatic cells is to inhibit glucose production (Coughlan et al., 2014), use of muscle cells or fat cells rather than HepG2 cells would be more relevant. Treatment of L6 myotubes with dipeptide WH significantly increased phosphorylation and activation of AMPKα, GLUT4 translocation to the plasma membrane, and glucose uptake into L6 myotubes. It has also been shown that activation of AMPKα occurs after transportation of WH into cells via the peptide transporter (Soga, Ohashi, Taniguchi, Matsui, & Tsuda, 2014).

2.8. Peptides promoting adipocyte differentiation

Adipose tissue has an important role in controlling whole-body glucose and lipid homeostasis in both normal and disease states by sequestering fat and producing various hormones and cytokines. Chronic excess calorie intake and the inability to generate new fat cells (adipocytes) may cause ectopic fat deposition, resulting in peripheral insulin resistance, particularly in skeletal muscle (Guilherme, Virbasius, Puri, & Czech, 2008). Decreased expression of adipogenic genes has been reported in obese subjects with type 2 diabetes (Dubois et al., 2006). Adipocyte differentiation generates new adipocytes with higher capacity for fat storage, and functional adipose tissue in proper proportion to body size is required for the normal insulin sensitivity and glucose homeostasis (Longo et al., 2019). Two key transcription factors in this process are the peroxisome proliferator-activated receptor-γ (PPARγ) and CCAAT/enhancer binding protein (C/EBP). PPAR-γ activates genes involved in adipocyte differentiation and fatty acid sequestration (Ahmadian et al., 2013). Several food-derived peptides have been reported to increase adipocyte differentiation *in vitro* and *in*

vivo. Milk-derived peptides, IPP and VPP, enhance adipocyte differentiation through upregulation of PPARγ and C/EBP-α. The effect of these peptides on adipocyte differentiation and adiponectin release was similar to insulin. IPP and VPP further exerted anti-inflammatory effects by inhibiting the cytokine mediated activation of the pro-inflammatory NF-κB pathway in adipocytes (Chakrabarti & Wu, 2015). Oral administration of VPP to C57BL/6J mice ameliorated diet-induced chronic inflammation in adipose tissue (Aihara, Osaka, & Yoshida, 2014; Sawada et al., 2015). High fat feeding resulted in the accumulation of activated monocytes and pro-inflammatory macrophages in the stromal vascular fractions of the adipose tissue, while VPP supplementation significantly reduced the pro-inflammatory status in adipose tissue (Aihara et al., 2014). VPP administration has also been reported to improve insulin sensitivity, reduce TNF-α and IL-1β expression, and macrophage accumulation and activation in diet induced obese mice (Sawada et al., 2015). Chlorella protein hydrolysate has shown favorable effects on glucose tolerance and insulin sensitivity in high-fat fed mice (Noguchi, Yanagita, Rahman, & Ando, 2016). Smaller adipocytes, lower triglycerides levels in liver, and reduced serum MCP-1 as well as MCP-1 mRNA expression in adipose tissue was correlated well with enhanced glucose tolerance and insulin sensitivity in chlorella hydrolysate-treated mice as compared to the control group. Considering the role of MCP-1 in development of inflammation and macrophage infiltration, less adipose tissue inflammation has been suggested as the key mechanism for the observed beneficial effects of chlorella-derived peptides in obese mice (Noguchi et al., 2016). In a similar vein, rice bran protein hydrolysate promoted the gene expression of PPARγ in adipose tissue of high carbohydrate-high fat fed rats similar to pioglitazone. Serum adiponectin was enhanced while adipose tissue inflammatory markers were decreased in rats treated with rice protein hydrolysate (Boonloh et al., 2015). We have recently shown the beneficial effects of egg white hydrolysate on adipocyte differentiation and insulin sensitivity in cell culture (Jahandideh et al., 2017, 2018) and animal studies (Jahandideh et al., 2019). Administration of egg white hydrolysate in insulin resistant rats reduced adipocyte size and increased PPARγ2 protein abundance in the adipose tissue, as well as reduced inflammation in these rats (Jahandideh et al., 2019). Despite the well-documented beneficial effects of enhanced PPARγ expression and adipocyte differentiation on insulin sensitivity, inhibition of adipocyte differentiation has been associated with beneficial outcomes. DIVDKIEI, an octapeptide derived from boiled tuna, has been reported to inhibit C/EBPs and PPARγ expression in 3T3-L1 adipocytes (Kim, Kim, Choi, Lee, & Nam, 2015). However, it should be noted that inhibition of adipocyte differentiation *per se* without affecting whole body energy balance is not beneficial for adipose tissue health and function. Inhibition of adipocyte differentiation could possibly result in the generation of hypertrophied adipocytes with less buffering capacity for circulating fats, and hence redistribution of body fat into non-adipose peripheral tissues in physiological conditions (Kim & Park, 2011). This would eventually lead to the development of insulin resistance in these tissues. Moreover, the hypertrophied adipocytes showed pro-inflammatory state due to the endocrine characteristics of the adipose tissue (Guilherme et al., 2008), which would result in the inactivation of insulin signaling and development of systemic insulin resistance. Whey peptides have been reported to promote adipocyte differentiation, PPARγ and PPARδ activation to increase lipid storage and oxidation, respectively. In myotubes, whey peptides ameliorate palmitate-induced inflammation, diacylglycerol accumulation and increase sequestration of fatty acids in the triglyceride pool, thereby countering insulin resistance (D'Souza et al., 2020). Table 2 summarizes the antidiabetic potential of protein hydrolysates/bioactive peptides through cell-based, animal studies as well as clinical trials.

3. Challenges on bioactive peptides research

The classical workflow for the production and discovery of bioactive peptides involves several steps as outlined in Fig. 2. This approach starts with identifying a suitable protein source, followed by steps to release bioactive peptide fragments, initial screening for a targeted bioactivity, multi-step fractionation procedures, identification of the peptide sequence, and ends with bioactivity validation using chemically synthesized pure peptides (Li-Chan, 2015). This classic approach for bioactive peptide discovery is often time consuming and costly. Moreover, commercialization of peptide discovery is challenging due to the low yield and purity of the peptides after extensive fractionation and isolation. Therefore, a feasible workflow that allows researchers to overcome these challenges is needed. Bioinformatics, referring to applied computational methods to manage, curate, and interpret information on biological systems, is becoming increasingly important in the discovery of food-derived bioactive peptides. These tools facilitate bioactive peptide discovery through the prediction of peptides' biological activity and optimization of classical procedures for their production. Therefore, bioinformatics provides a cost-effective strategy in the discovery of bioactive peptides by reducing steps in the traditional workflow (Li-Chan, 2015; Sánchez-Rivera, Martínez-Maqueda, Cruz-Huerta, Miralles, & Recio, 2014). Artificial intelligence (AI) which includes machine learning approaches, has been recently employed in the discovery of food-derived bioactive peptides (Kennedy et al., 2020; Rein et al., 2019). An AI approach to discover a functional ingredient capable of modulating glucose levels was utilized by Chauhan and co-workers. Following prediction of pea (*P. sativum*) as an optimal plant source of bioactive peptides with glucoregulatory properties, NRT_N0G5IJ (PeptiForce™) was produced, and its activity and safety was validated in human skeletal muscle cells. The antidiabetic effects of this peptide were then further confirmed in a diabetic murine model followed by a clinical trial carried in a prediabetic population (Chauhan et al., 2021).

Considering the potential effect of exopeptidases on peptide digestion by these methods can further improve their power in predicting the release of peptides with both *in vitro* and *in vivo* biological properties (Sato, 2018). After discovery and production of peptides either through in-silico or classical approaches, evaluation of the biological activity of peptides *in vivo* is critical. Many studies in this area rely on *in vitro* and cell-based assays for identification of peptides and assessment of biological activities. *In vivo* assessment of bioactive peptides has been done, but these are uncommon, and clinical studies for validation of bioactive peptides effectiveness in humans are even more scarce. The sparse data on bioavailability and metabolic fate of bioactive peptides *in vivo* is a major challenge in the field of bioactive peptides' research. Additionally, information on absorption, distribution, metabolism, and excretion of bioactive peptides is critical. Susceptibility of the peptides to degradation by gastric, pancreatic, and small intestinal brush border membrane enzymes has not been considered in majority of the research on bioactive peptides especially for the peptides which exert their bioactivity via the systemic circulation. Considering the harsh condition of the gastrointestinal tract during digestion as well as food matrix and interactions between food components (especially between peptides and polyphenols) (Perez-Gregorio, Soares, Mateus, & de Freitas, 2020), it is likely that only minute quantities of the bioactive peptides pass into the systemic circulation, which may be insufficient to induce biological activity. Indeed, food-derived peptides usually present in the body as di- or tripeptides at concentrations of up to 100 μM (Sato, 2017, 2018). Whether ingestion of these peptides or the hydrolysate containing them would result in the release of peptides which are active at these concentrations, or whether they are turned into non-active metabolites is an important issue to consider. To account for the shortcomings of the *in vitro* activity-guided fractionation approach for peptides' bioavailability, Sato has recently proposed a new approach for identification of bioactive peptide in the target organ first followed by an examination of their *in vitro* and *in vivo* activities (Sato, 2018). Pre-identification of peptides present in the *in vitro* exopeptidase digests of food peptide is helpful for identification of the food-derived peptides in the body.

Due to the bitter taste of peptides, successful implementation of

Table 2
Some examples of food-derived bioactive peptides/protein hydrolysates with antidiabetic properties (cell-based, *in vivo*, and human studies).

Source	Treatments	Identified peptides	Observed effect/Mechanism of action	Model	Reference
Hard-to-cook common beans (Black 8025, Pinto Durgo)	Alcalase or bromelain	Peptides < 1 kDa, FFL, QLGGH, LLSL, WGVFN, RFEFLMLLGQ, LLLLEDRRR, EPHGK, HVQNQ, NDEPASG	DPP-IV inhibition, increase insulin secretion, improve insulin signalling, enhance insulin-induced glucose uptake via Akt modulation	Pancreatic β-cells, adipocytes, *in vitro*	Toledo, de Mejia, Sivaguru, and Amaya-Llano (2016)
Black bean protein isolate	Alcalase	AKSPLF, ATNPLF, FEELN, and LSVSVL	Blocking GLUT2 and SGLT1 (reduce glucose absorption), reduce fasting and postprandial glucose levels	Caco-2 cells, *in-silico*, healthy and diabetic rats	Mojica et al. (2017)
Pea protein	Synthetic peptides	VLP, LLP, LL, LL	Increase hepatic glucose absorption and consumption through IRS-1/PI3K/AKT and p38MAPK pathways. Increase GLUT2 gene expression and protein content (LLP, VA, LL), decrease intracellular ROS and TNF-α (VLP, LL)	Insulin resistant HepG2 cells	Zhu et al. (2020)
Pea protein	Alcalase and neutrase	ALP, VLP, LLP, SP	Reducing blood glucose levels, improving glucose tolerance, promoting insulin release and glycogen synthesis, and protecting liver and kidney structures	High fat fed and streptozotocin (STZ)-induced diabetic mice	Wei et al. (2019)
Pea protein	Food-grade serine protease	NRT_N0G5IJ (peptides between 7 and 16 amino acids, with net charge of + 1. Most peptides contained 40% hydrophobic residues)	Increase glucose uptake, reduction in glycated haemoglobin (HbA1c) levels reducing fasting glucose	Human skeletal muscle cells, db/db diabetic mice, and clinical (double-blinded, placebo controlled human trial)	Chauhan et al. (2021)
Foxtail millet protein	Raw and cooked protein isolates	Not determined	Hypoglycemic effects through rewiring glucose homeostasis, mitigating diabetes-induced gut dysbiosis. The cooked foxtail millet protein isolate affected the GLP-1R/PI3K/AKT pathway and reversed the weight loss trend and alleviated lipid disorders in diabetic mice	STZ-induced diabetic mice	Fu et al. (2021)
Wheat gluten	Commercial protein hydrolysate (HyPep 4601)	Not determined	Suppression of food intake in healthy rats, elevating plasma PYY levels, stimulation of CCK and GLP-1 in enteroendocrine cells	Enteroendocrine cell lines (STC-1 cells and GLUTag cells), and Wistar rats	Chen, Hira, Nakajima, and Hara (2018)
Walnut	Neutrase and alcalase	LVRL, LRYL, VLLALVLLR	Improve glucose consumption, glucose uptake, and GLUT4 translocation, elevation of p-IRS-1 and p-Akt. Inhibition of glucose-induced insulin resistance by activating IRS-1/PI3K/Akt and Nrf2/HO-1 signaling pathways	HepG2 cells	Wang et al. (2020b)
Walnut	Alcalase	LPLLR	α-glucosidase and α-amylase inhibition, improving hepatic insulin resistance, increase glycogen synthesis and glucose uptake, decrease gluconeogenesis via activating the IRS-1/PI3K/Akt and AMPK signal pathways	Glucose induced insulin resistant HepG2 cells	Wang et al. (2020a)
Walnut	Neutrase and alcalase	Peptide fractions with 3–10 KDa	α-glucosidase inhibition, increase in extracellular glucose consumption, reduce fasting blood glucose, increase in insulin secretion, liver glucokinase and glycogen levels	Insulin-resistant HepG2 cells, STZ-induced diabetic mice	Wang et al. (2018)
Egg white protein	Thermolysin and pepsin	WEKAFKDED, QAMPFRVTEQE, ERYPIL, VFKGL	Enhance pre-adipocyte differentiation, show insulin mimetic and sensitizing effects (Akt and ERK1/2 phosphorylation), improve glucose uptake, glucose tolerance, and reduce systemic inflammation, reduce adipocyte size and increased PPARγ2 protein abundance and activity	3T3-F442A pre-adipocytes and diet-induced insulin resistant rats	de Campus Zani et al. (2019), Jahandideh et al. (2017), Jahandideh et al. (2018), and Jahandideh et al. (2019)
Egg protein (lysozyme)	Alcalase	Not determined	Decrease in glucose and insulin levels	Overweight and obese subjects with impaired glucose tolerance or type 2 diabetes	Plat, Severins, and Mensink (2019)
Boarfish protein	Alcalase, and flavourzyme	Twenty two DPP-IV inhibitory peptides, fifteen insulinotropic peptides. IPVDM and IPV (the most active)	DPP-IV inhibition, insulinotropic activity	*In vitro*, Caco2 cells and pancreatic BRIN-BD11 cells	Harnedy-Rothwell et al., 2020
Blue whiting		Not determined			Harnedy et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Source	Treatments	Identified peptides	Observed effect/Mechanism of action	Model	Reference
	Alcalase and flavourzyme, simulated gastrointestinal digestion (pepsin and corolase PP)		Reducing blood glucose, DPP-IV inhibition, enhancing insulin and GLP-1 release. Simulated gastrointestinal digestion enhanced GLP-1 secretion, increased membrane potential, intracellular calcium and cyclic AMP concentration versus a glucose control	BRIN-BD11 and GLUTag cells, healthy male NIH Swiss mice	
Marine collagen	Pepsin, trypsin, chymotrypsin, pancreatic lipase	Not determined	Reduce fasting blood insulin and glucose, HbA1c, increase insulin sensitivity. Reduce hs-CRP and NO, increase bradykinin, PGI2, and adiponectin	Chinese patients with type 2 diabetes	Zhu et al. (2010)
Cod protein	Protamex® (Novozymes AS)	Not determined	Reduce postprandial insulin secretion without affecting blood glucose response or GLP-1 levels in younger adults. Serum glucose and insulin levels in older adults tend to decrease with increasing amounts of cod protein hydrolysate	Healthy individuals (young and old)	Dale et al. (2018) and Jensen et al. (2019)
Sea cucumber	Papain and protamex	Not determined	Improving glucose tolerance and insulin resistance in diabetic rats. Reduce fasting blood glucose level. Increase expressions of PI3K, p-Akt, p-GSK-3β and GLUT2/GLUT4 in liver and skeletal muscle of diabetic rats	High fat fed and STZ-induced diabetic Sprague Dawley rats	Wang et al. (2020)
Whey protein	Protease enzymes from *Bacillus subtilis* and *Aspergillus oryzae*	IV, LV, VL, II, LI, IL, LL	Increase glucose uptake and glycogen synthesis	L6 myotubes and isolated skeletal epitrochlearis muscles	Morifuji, Koga, Kawanaka, & Higuchi, 2009
Casein	Food grade gastrointestinal enzymes (pepsin and pancreatin)	Not determined	Reducing blood glucose and lipid, more responsive to glucose in glucose-stimulated insulin secretion. In human trial, increase in insulin secretion t with a reduction in glucose was observed, while no effect on c-peptide or GIP secretion was noted	Male mice (ob/ob and C57BL/6), healthy overweight/obese Caucasian adults	Drummond et al. (2018)
Horn beetle	Ethanol extract	Not determined	Inhibition of adipogenesis and lipogenesis, reduce serum triglyceride and leptin contents	3T3-L1 adipocytes; high fat diet-fed mice	Chung, Yoon, Hwang, Goo, and Yun (2014) and Yoon et al. (2015)
Horn beetle	Dried ethanol extracts	Not determined	Reducing hypothalamic endoplasmic reticulum stress, body weight and apetite through mTOR ad MAPK signaling pathways	High fat diet obsese mice	Kim, Yun, Park, Goo, and Seo (2016)
Yellow mealworm larvae	Water and dried ethanol extracts	Not determined	Inhibition of adipogeneiss through AMPK and MAPK signaling, reduce body weight gain, fat mass, adipocyte size as well as hepatic steatosis	3T3-L1 adipocytes and high fat diet obese mice	Seo et al. (2017)

bioactive peptides as functional food ingredients relies on enhancing the organoleptic properties of peptides. Moreover, development of new tools for the prediction and evaluation of peptides bitterness can potentially pave the road in commercialization of bioactive peptides in food industry. Partial least square regression models constructed with the e-tongue and the combination of size exclusion chromatography and reversed-phase HPLC have been used recently for the prediction of bitterness of dairy protein hydrolysates (Newman et al., 2014). Adoption of such models has the potential to reduce the reliance of bioactive peptides on sensory analysis in future studies.

Finally, successful translation of discoveries in the field of bioactive peptides to viable health promoting products requires a thorough understanding of the evolving regulatory environment. One important step would be defining products containing bioactive compounds precisely and avoid using imprecise and overly broad terminology (e.g. functional foods, novel foods, foods for special uses, supplemented foods etc.).

Placing novel formulations of bioactive peptides in their appropriate place within the food-drug continuum is critical in establishing appropriate standards for manufacturing of such products, their quality control and health claims as well as audit purposes in order to develop commercial products (Chakrabarti, Guha, & Majumder, 2018).

4. Conclusions

Development and discovery of bioactive peptides for use in the treatment of diabetes is a growing research field. The recent discoveries in the field of bioactive peptides and their potential effects on pathways and target cells in the management of glucose and energy metabolism presents new opportunities for the use of such peptides in enhancing adipocyte differentiation and insulin signaling, CCK receptor binding and expression, and incretin stimulants, to name a few. However, there is a paucity of evidence related to the efficacy of such bioactive peptides in models of diabetes, and more research is required to validate their potential benefits *in vivo*. Furthermore, clinical studies are also required to evaluate the physiological effects of antidiabetic food-derived peptides in human. Lack of scalable, cost-efficient, and consistent techniques to produce bioactive peptides, the unknown impact of the food matrix on absorption and bioavailability of bioactive peptides, and scarce data on pharmacokinetic and pharmacodynamics of bioactive peptides are some of the challenges associated with the commercialization and utilization of food-derived bioactive peptides for their health benefits. Taste and other sensory attributes of the final product containing bioactive peptides also need to be considered for successful adoption of peptides as functional food ingredients that can improve health and promote resilience.

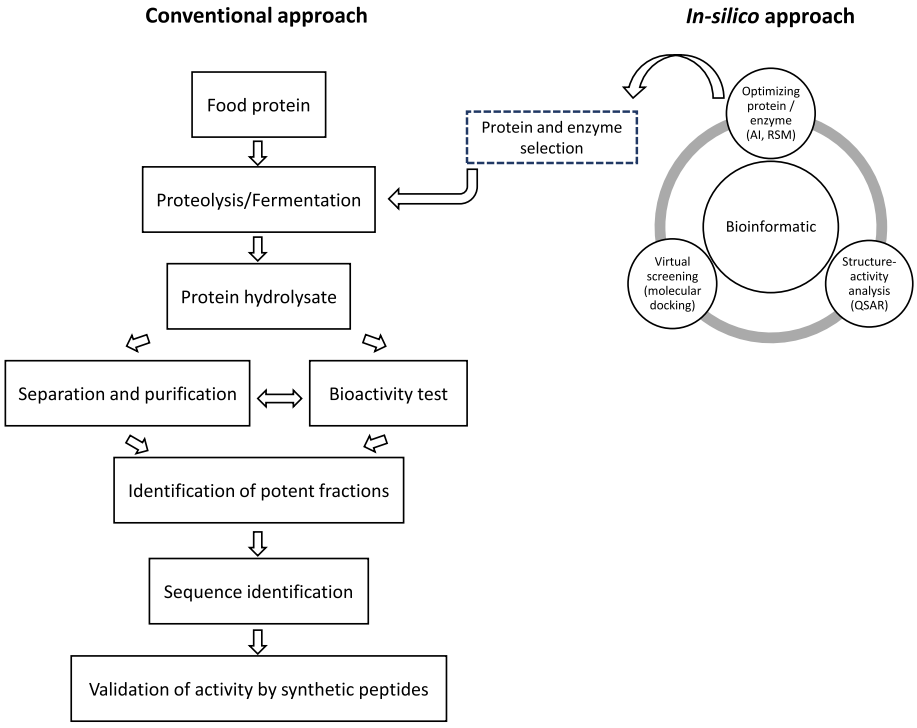

Fig. 2. The classical and *in-silico* approaches for the production and discovery of bioactive peptides from food proteins. AI: artificial inteligence; RSM: response surface methodology; QSAR: quantity structure activity relationship.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jianping Wu reports financial support was provided by Natural Sciences and Engineering Research Council of Canada. Jianping Wu reports financial support was provided by Alberta Agriculture and Forestry, Food And Bio Processing Branch. Jianping Wu reports financial support was provided by Egg Farmers of Canada.

Acknowledgments

The laboratory of Jianping Wu is supported by Grants from Natural Sciences and Engineering Research Council (NSERC) of Canada, Alberta Agriculture and Forestry, and Egg Farmers of Canada.

Author Contributions

Conceived and designed the idea for the manuscript: Forough Jahandideh, Stephane Bourque, and Jianping Wu; Wrote the manuscript draft: Forough Jahandideh; Revised the manuscript: Stephane Bourque and Jianping Wu.

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