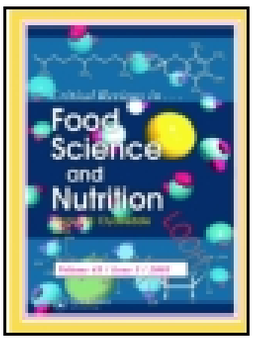

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REVIEW



# Bioactive peptides in the management of lifestyle-related diseases: Current trends and future perspectives

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**ABSTRACT**

Lifestyle-related diseases constitute a major concern in the twenty-first century, with millions dying worldwide each year due to chosen lifestyles and associated complications such as obesity, type 2 diabetes, hypertension, and hypercholesterolemia. Although synthetic drugs have been shown to be quite effective in the treatment of these conditions, safety of these compounds remains a concern. Natural alternatives to drugs include food-derived peptides are now being explored for the prevention and treatment of lifestyle-related complications. Peptides are fragments nascent in the primary protein sequences and could impart health benefits beyond basic nutritional advantages. Evidence suggests that by controlling adipocyte differentiation and lipase activities, bioactive peptides may be able to prevent obesity. Bioactive peptides act as agents against type 2 diabetes because of their ability to inhibit enzymatic activities of DPP-IV, α-amylase, and α-glucosidase. Moreover, bioactive peptides can act as competitive inhibitors of angiotensin-converting enzyme, thus eliciting an antihypertensive effect. Bioactive peptides may have a hypocholesterolemic effect by inhibiting cholesterol metabolism pathways and cholesterol synthesis. This review addresses current knowledge of the impact of food-derived bioactive peptides on lifestyle diseases. In addition, future insights on the clinical trials, allergenicity, cytotoxicity, gastrointestinal stability, and regulatory approvals have also been considered.

**KEYWORDS**

Bioactive peptides; lifestyle diseases; obesity; Type-2 diabetes; hypertension; hypercholesterolemia

## 1. Introduction

Proteins are well known for their comprehensive nutritional, functional, and biological properties. Amino acids are primarily essential for physical development, growth, maintenance, repair and proper functioning of body organs and cells (Manikkam et al. 2016). To exert biological effects, dietary proteins must be digested into peptides and amino acids, which are then absorbed in sufficient concentrations into blood circulation. Bioactive peptides that are encrypted in the primary sequences of proteins can be released by the action of exogenous and endogenous proteolytic enzymes or microbial fermentation or during food processing. Although, enzymatic hydrolysis is the most common approach to generate bioactive peptides from whole food proteins, the use of fermentation is primarily relevant to the products which naturally contain precursor proteins such as milk, soy milk and some other aqueous products. After protein hydrolysis, peptides need to be purified and characterized using empirical approaches. Finally obtained peptides tested for the targeted bioactivities using in vitro, in vivo and human studies (Singh and Vij 2017; Singh, Vij, and Hati 2014) (Figure 1).

In order to reach their target organs, bioactive peptides must be absorbed; small peptides (di- and tri-peptides) are more efficiently absorbed than larger ones, which are prone to hydrolysis by enterocyte peptidases (Bouglé and Bouhallab 2017). These small bioactive peptides posses low molecular weight, high bioavailability, and flexible molecular structure that allow them to interact easily with different receptors in vitro and within the human body (Martínez-Sánchez, Gabaldón-Hernández, and Montoro-García 2020). Bioactive peptides are considered to promote diverse activities, including antimicrobial, antioxidant, antihypertensive, immunomodulatory, hypocholesterolemic, opiate-like, mineral binding and antithrombotic (Singh and Vij 2018; Singh and Vij 2017; Singh et al. 2015; Singh, Vij, and Hati 2014; Malaguti et al. 2014). During digestion, the bioactive peptides can be absorbed through the digestive system to enter the blood circulation and exert systemic effects (Saadi et al. 2015). In recent years, the isolation, identification and characterization of bioactive peptides have become emerging research subjects (Sánchez-Rivera et al. 2014). As a component of functional foods or nutraceuticals with certain health claims, bioactive peptides are of commercial interest as well.

Epidemics of lifestyle-related diseases are the result of increasingly poor dietary habits of modern society. Unhealthy practices can deviate people from healthy activities and strike them to an inactive schedule which leads to numerous health diseases that can lead to chronic non-communicable diseases that can have near life-threatening consequences (Tabish 2017). Lifestyle-related diseases such

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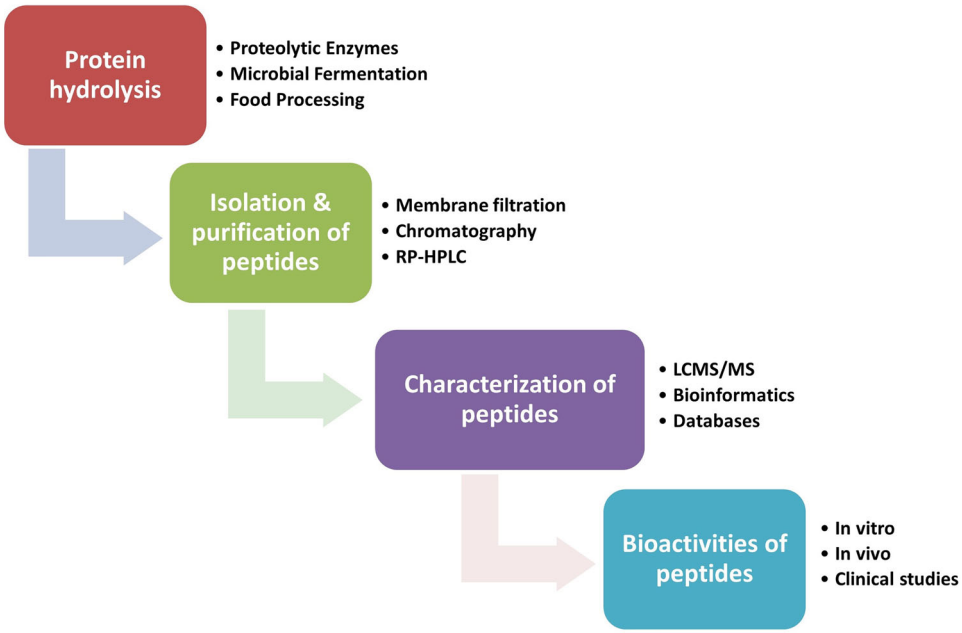


**Figure 1.** Schematic representation of production, purification, characterization, and bioactivities analysis of bioactive peptides.

as obesity, type 2 diabetes, hypertension, and hypercholesterolemia have become a major concern of the twenty-first century. Millions of people are dying globally every year due to lifestyle and its associated complications (Van Zyl et al. 2012). Cardiovascular diseases, a chronic conditions of lifestyle disease, are the world's leading single cause of death. A World Health Organization (WHO) report showed that every year more than 17 million people die from cardiovascular diseases (Wang et al. 2016). High blood pressure, smoking, diabetes, lack of exercise, obesity, high cholesterol in the blood, poor diet, and excessive alcohol consumption can induce these diseases.

In spite of diverse variety of existing drugs, the prevalence of lifestyle diseases are exponentially increasing, and predictions suggests it will rise to 333 million by 2025 (Silveira et al. 2013). Although, few drugs have proved to be quite effective in some of these conditions, the safety issues associated with these compounds are believed to be due to their unnatural molecular structures. Therefore, natural alternatives need to be identified for the prevention and treatment of these disorders. One of the major advantages of natural compounds is they commonly do not show serious side effects. Food-derived peptides are a group of natural compounds currently being studied for the prevention and the treatment of obesity, hypertension, type-2 diabetes, hypercholesterolemia and related disorders. Inhibition of various enzymes, especially metabolic enzymes, may be an important function of bioactive peptides in preventing and treating these diseases (Lafarga and Hayes 2014).

In terms of technological and functional properties, bioactive peptides have been widely studied but only a few studies have been able to evaluate their effects on human subjects. The discovery of bioactive peptides with potent efficacy in human subjects, along with their safety and regulatory consideration, is very critical for commercialization purposes. This review provides the current status of food-derived bioactive peptides in the management of some lifestyle disorders such as obesity, type 2 diabetes, hypertension, and hypercholesterolemia. Besides, the future direction for other important factors such as allergenicity, safety, bioavailability, and regulatory requirements are also discussed.

## Bioactive peptides in management of obesity

Obesity is a medical condition, characterized by an excessive accumulation of fat in adipose tissues arising from excess calorie intake due to a discrepancy between energy intake and energy usage. Obesity is usually associated with other metabolic diseases, including type 2 diabetes, hypertension, cancer, and cardiovascular diseases (Wang et al. 2020a). An excess of body fat is well known to induce chronic inflammation, insulin resistance, and impair insulin secretion (Moreno-Valdespino et al. 2020). Proteins are well known nutrients that accelerate caloric metabolism. A number of study models have demonstrated the anti-obesity effect that protein hydrolysates or bioactive peptides can exert, for example, controlling the differentiation of adipocytes can be a critical strategy to prevent or treat obesity (Figure 2). One explanation for protein impact on weight loss is that peptides released during gastrointestinal digestion initiate satiety signals from the gut and suppress food intake (Iwaniak, Darewicz, and Minkiewicz 2018). An animal study suggested that obesity can be prevented by whey protein, α-lactalbumin and lactoferrin (Shi et al. 2012a; Shi et al. 2012b). A human study also demonstrated regulation of body fat mass and lean muscle after ingestion of whey protein concentrate before the main intake of meals (Tahavorgar et al. 2014). In overweight subjects that consumed 300 mg/day of lactoferrin for 8 weeks, significant reductions in visceral fat, body weight, and BMI were found (Bouglé and Bouhallab 2017). Obesity can be managed by targeting an integrated signaling network among gut hormones, neuropeptides, and the

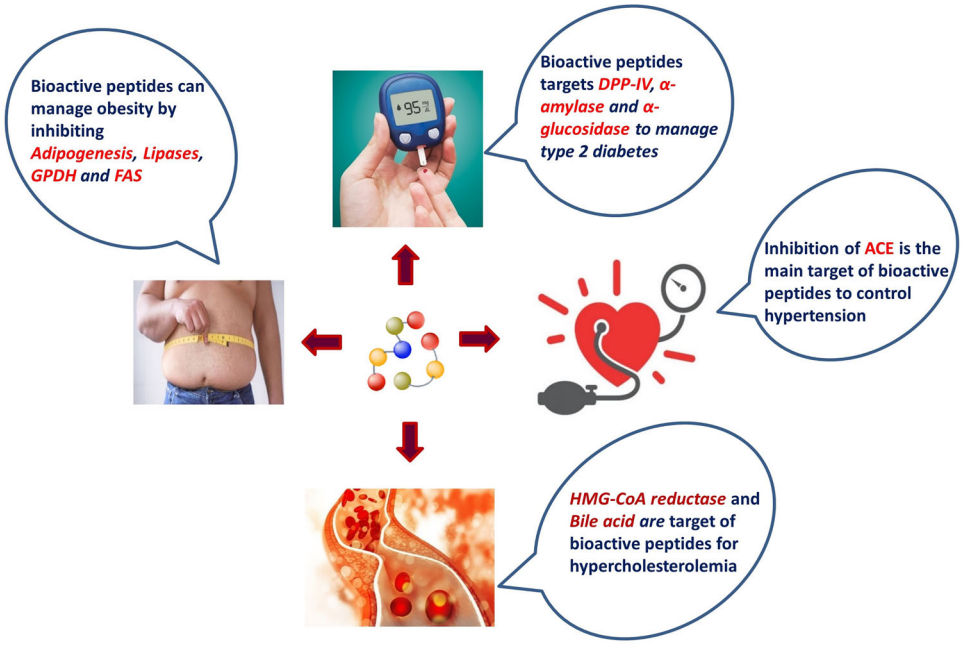


**Figure 2.** Current strategies to manage common lifestyle-related disease by the use of bioactive peptides.

central nervous system, which are involved in appetite, gastric emptying, gastric acid secretion, and energy expenditure (Lai, Wu, and Pan 2015).

Adipose tissues play an important role in energy homeostasis, insulin sensitivity and lipid metabolism (Li et al. 2015). An increase in the size and number of adipose tissue is associated with metabolic dysfunctions that lead to dysregulated production of markers associated with pro-inflammatory factors and obesity such as tumor necrosis factor, interleukin, plasminogen activator inhibitor, resistin, leptin and adiponectin, leading to the activation of inflammatory signaling pathways and oxidative stress (Fasshauer and Blüher 2015; Moreno-Valdespino et al. 2020). Adipogenesis is controlled by the peroxisome proliferator-activated $\gamma$ receptor (PPAR$\gamma$) and the CCAAT/enhancer-binding $\alpha/\beta/\delta$ protein. The PPAR$\gamma$ activation promotes differentiation of preadipocytes into mature adipocytes (Li et al. 2018). Therefore, obesity may be controlled by reducing adipogenesis through inhibition of PPAR$\gamma$ activity or reducing preadipocyte differentiation. In this regard, recently a novel anti-obesity peptide (RLLPH) derived from hazelnut protein hydrolysates has been found to attenuate adipogenesis by downregulating mRNA expression of adipogenesis-related factors and enzymes such as PPAR$\gamma$, C/EBP$\alpha$, aP2, SREBP-1c, FAS, ACC1, and HMGCR in mouse 3T3-L1 preadipocytes cell culture (Wang et al. 2020a) (Table 1). Four peptides, NALKCCHSCPA, LNNPSVCDCDCMMKAAR, NPVWKRK and CANPHELPNK, from *Spirulina platensis* were also reported to have inhibitory effects (32.29-60.08%) on mouse 3T3-L1 preadipocytes cell (Fan et al. 2018). Whey protein has also been found to inhibit PPAR$\gamma$ expression and lipid accumulation in 3T3-L1 preadipocytes and to reduce body weight in high fat-fed rats. Similarly, it has also been observed that soy protein hydrolysate and casein glycomacropeptides inhibit the accumulation of fat in primary and 3T3-L1 adipocytes, respectively (Martinez-Villaluenga et al. 2009; Rajic et al. 2010; Xu et al. 2011; Li et al. 2018). Moreover, based on their findings in obese Zucker rats, Drotningsvik et al. (2016) concluded that diets containing hydrolyzed residue raw material from herring or salmon proteins affect growth, lipid metabolism, postprandial control of glucose and the composition of fatty acids in the serum and adipose tissue.

Furthermore, pancreatic lipases (PL & PLA2) are the main secreted enzymes responsible for the breakdown and absorption of 50-70% of dietary fats (Sreerama, Takahashi, and Yamaki 2012; Birari and Bhutani 2007; Shi and Burn 2004) (Figure 2). Several studies have found that phosphatidylcholine hydrolysis by PLA2 is necessary for the successful absorption of fatty acids, cholesterol and other hydrophobic lipids (Wang, Noh, and Koo 2006). Inhibitions of PL and PLA2 have been the most effective mechanisms to reduce the gastrointestinal absorption of dietary fat, thus reducing the effect of obesity. The *Spirulina platensis* peptides, NPVWKRK and CANPHELPNK, showed in vitro inhibitory effects on pancreatic lipase, which decreased triglyceride accumulation at 600 µg/ml, up to 23.7% and 19.5%, respectively (Fan et al. 2018). Mudgil et al. (2018) also reported in vitro pancreatic lipase inhibitory effect of peptides derived from camel milk protein hydrolysates.

Moreover, glycerol-3-phosphate dehydrogenase (GPDH) is a crucial enzyme in the metabolism of glucose, phospholipids and biosynthesis of triglycerides, capable of preventing differentiation and aggregation of lipids in pre-adipocyte cells. In 3T3-L1 pre-adipocyte cells, addition of a soy protein alcalase hydrolysate led to 29.0 – 46.0% decrease in lipid accumulation (Martinez-Villaluenga et al. 2008; de Castro and Sato 2015). Similarly, fatty acid synthase (FAS), which plays a key role in the endogenous synthesis of saturated long-chain acetyl-CoA and malonyl-CoA precursor fatty acids can be measured to assess anti-adipogenic effects (de Castro and Sato 2015). Three peptides, KNPQLR,

**Table 1.** List of bioactive peptides recently identified from food proteins for the management of lifestyle-related diseases (in vitro and in vivo animal studies).

| Source of peptide | Peptide sequences | Study model | Result/ activity | Effect | Reference |
|---|---|---|---|---|---|
| Hazelnut protein | RLLPH | In vitro (3T3-L1 preadipocytes cell culture) | Inhibit adipogenesis by downregulating mRNA expression of adipogenesis-related factors and enzymes | Antiobesity | Wang et al. 2020a |
| *Spirulina platensis* Fan et al. 2018 | NALKCCHSCPA, | LNNPSVCDCDCMMKAAR, NPVWKRK, CANPHELPNK | In vitro (3T3-L1 preadipocytes cell culture) | Inhibition of preadipocytes cell proliferation by32.29-60.08%) | Antiobesity |
| *Spirulina platensis* | NPVWKRK, CANPHELPNK, | In vitro (enzyme assay) | Inhibitory effects on pancreatic lipase | Antiobesity | Fan et al. 2018 |
| *Phaseolus vulgaris* Jakubczyk et al. 2017 | INEGSLLLPH, FVVAEQAGNEEGFE, | SGGGGGGVAGAATASR, GSGGGGGGGFGGPRR, GGYQGGGYGGNSGGGYGNRG, GGSGGGGGSSSGRRP, GDTVTVEFDTFLSR | In vitro (enzyme assay) | Lipase inhibition | Antiobesity |
| Soybean | ILL, LLL, VHVV | In vitro (3T3-L1 preadipocytes cell culture) | lipolysis-stimulating activity (lipolysis of triglyceride in the adipocytes has been considered as a potential therapeutic target for obesity) | Antiobesity | Tsou et al. 2013 |
| Soybean | VHVV | In vivo (mice fed a high fat diet) | Regulated TNF-$\alpha$ expression, which was elevated due to a high fat diet and suppressed apoptosis-related proteins. | Antiobesity | Asokan et al. 2018 |
| Synthetic peptide | PDBSN | In vitro & in vivo (high-fat diet induced obese mice) | Suppress adipogenesis, reduce weight gain, improve insulin resistance as well as lipid homeostasis | Antiobesity | Shen et al. 2019; Shen et al. 2020 |
| Whey | LDQWLCEKL | In vitro (enzyme assay) | Inhibit DPP-IV ($IC_{50}$ = 131 $\mu$M) | Anti-diabetic | Jia et al. 2020 |
| *Spirulina platensis* | LRSELAAWSR | In vitro (enzyme assay) | DPP-IV inhibition ($IC_{50}$ = 167.3 $\mu$g/ml),$\alpha$-glucosidase inhibition ($IC_{50}$ = 134.2 $\mu$g/ml), $\alpha$-amylase inhibition ($IC_{50}$ = 313.6 $\mu$g/ml) | Antidiabetic | Hu et al. 2019 |
| *Sardine pilchardus* muscle | NAPNPR, YACSVR | In vitro (enzyme assay) | DPP-IV inhibition ($IC_{50}$ − 1.83 mg/ml) | Antidiabetic | Rivero-Pino, Espejo-Carpio, and Guadix 2020 |
| Camel milk | LAHKPL, VPV, YPI, VPF | In vitro (enzyme assay) | DPP-IV inhibition ($IC_{50}$ values of 239.7, 6.6, 35.0 and 55.1 $\mu$M, respectively) | Antidiabetic | Nongonierma et al. 2019 |
| Salmon skin collagen | LDKVFR | In vitro (enzyme assay) | Inhibit DPP-IV ($IC_{50}$ = 0.1 mg/ml). | Antidiabetic | Jin et al. 2020 |
| Quinoa | IQAEGGLT | In vitro (enzyme assay) | 17.5% (DPP-IV) and 55.85% ($\alpha$-glucosidase) inhibition at 250 $\mu$M peptide concentration | Antidiabetic | Vilcacundo, Martınez-Villaluenga, and Hernandez-Ledesma 2017 |
| Silver carp | LPIIDI, APGPAGP | In vitro (enzyme assay) | DPP-IV inhibitory activity with $IC_{50}$ values of 105.44 and 229.14 $\mu$M, respectively | Antidiabetic | Zhang et al. 2016 |
| *Palmaria palmata* | ILAP, LLAP | In vitro (enzyme assay) | DPP-IV inhibition with $IC_{50}$ values in the 43–159 $\mu$M range | Antidiabetic | Harnedy, O'Keeffe, and FitzGerald 2015 |
| Walnut protein | LPLLR | In vitro (enzyme assay) | Inhibit $\alpha$-glucosidase (50.12%) and $\alpha$-amylase (39.08%) at concentration of 2000 $\mu$M | Antidiabetic | Wang et al. 2020b |
| Egg yolk | VTGRFAGHPAAQ | In vitro (enzyme assay) | $\alpha$-glucosidase inhibition with $IC_{50}$ value of 365.4 $\mu$g/ml | Antidiabetic | Zambrowicz et al. 2015 |
| Cumin seed Siow, Lim, and Gan 2017 | | RCMAFLLSDGAAAAQQLLPQYW, DPAQPNYPWTAVLVFRH | In vitro (enzyme assay) | Inhibition of bacterial and human salivary $\alpha$-amylases was with $IC_{50}$ values of 0.11 and 0.04 $\mu$M, and 0.10 and 0.15 $\mu$M, respectively | Antidiabetic |

| | | | | | |
|---|---|---|---|---|---|
| Lupin proteins | LTFPGSAED | In vitro (enzyme assay on caco-2 cells) and in vivo assay on human serum samples | DPP-IV inhibition with $IC_{50}$ value of 207.5 μM | Antidiabetic | Lammi et al. 2018 |
| Soybean | IAVPTGVA | In vitro (enzyme assay on caco-2 cells) and in vivo assay on human serum samples | DPP-IV inhibition with $IC_{50}$ value of 223.2 μM | Antidiabetic | Lammi et al. 2018 |
| Bovine β-casein | LPQNIPPL | In vitro (enzyme assay) and in vivo (rat) | DPP-IV inhibition ($IC_{50}$ = 4.6 μM) and blood glucose concentrations were suppressed by oral administration to rats (30 mg/kg body weight) | Antidiabetic | Uenishi et al. 2012 |
| Sheep cheese whey | LAFNPTQLEGQCHV | In vitro (enzyme assay) | ACE inhibition (55%) | Antihypertensive | Corrêa et al. 2014 |
| Palm kernel cake | YLLK, YGIKVGYAIP, LPWRPATNVF | In vitro (enzyme assay) | ACE inhibition (100%) | Antihypertensive | Zarei et al. 2015 |
| Horse gram hydrolysate | TVGMTAKF, QLLLQQ | In vitro (enzyme assay) | ACE inhibition with $IC_{50}$ values of 30.3 and 75.0 μM, respectively | Antihypertensive | Bhaskar, Ananthanarayan, and Jamdar 2019 |
| Porcine muscle | EKERERQ, KRQKYDI | In vitro (enzyme assay) | ACE inhibition with $IC_{50}$ values of 552.5 and 26.2 μM, respectively | Antihypertensive | Katayama et al. 2008; Lafarga and Hayes 2014 |
| Tomato | DGVVYY | In vitro (enzyme assay) | ACE-inhibitory activity with an $IC_{50}$ value of 2 μM | Antihypertensive | Moayedi et al. 2018 |
| Soybean protein isolates | EDEVSFSP, SRPFNL, RSPFNL, ENPFNL | In vitro (enzyme assay) | ACE-inhibitory activity with $IC_{50}$ values of 0.571, 0.131, 0.811 and 0.287 mg/mL, respectively | Antihypertensive | Daliri et al. 2018a |
| Walnut residue extract | VQTL, LGYEN | In vitro (enzyme assay) | ACE-inhibitory activity | Antihypertensive | Zheng, Li, and Ding 2017 |
| Wheat gluten hydrolysate | SAGGYIW, APATPSFW | In vitro (enzyme assay) | ACE-inhibitory activity with $IC_{50}$ values of 0.002 and 0.036 mg/mL, respectively | Antihypertensive | Zhang et al. 2020a |
| *Sargassum maclurei* | RWDISQPY | In vitro (enzyme assay) and in vivo using spontaneously hypertensive rats (SHRs) | ACE inhibition ($IC_{50}$ 72.24 μM) and lower blood pressure (150 mg/kg body weight) | Antihypertensive | Zheng, Zhang, and San 2020 |
| Egg white | QIGLF, RVPSL | In vivo (SHRs) | 48 and 46 mmHg decreases in systolic blood pressure, respectively | Antihypertensive | Yu et al. 2020 |
| Mushroom (*Tricholoma matsutakei*) | WALKGYK | In vitro (enzyme assay) and in vivo (SHRs) | ACE inhibition ($IC_{50}$ = 0.40 μM) and lower blood pressure (25 mg/kg dose) | Antihypertensive | Geng et al.2016 |
| Mung bean | LRLESF, YADLVE | In vitro (enzyme assay) and in vivo (SHRs) | ACE inhibition ($IC_{50}$ = 5.4 μM) and lower blood pressure (-27 mmHg) | Antihypertensive | Sonklin et al. 2020 |
| Egg white | IQW, LKP | In vivo (SHRs) | Decreased mean blood pressure | Antihypertensive | Majumder et al. 2015 |
| Milk | TDVEN, LQPE, VAPFPE, VLPVPQ | In vitro and in caco-2 cell model | Reduction in the solubility of micellar cholesterol and negative effects on the expression of proteins and enzymes related to cholesterol absorption | Hypocholesterolemic | Jiang et al. 2020 |
| Cowpea bean | GCTLN | In vitro | Inhibited HMG-CoA reductase | Hypocholesterolemic | Marques et al. 2015 |
| *Miichthys miiuy* muscle | VIAPW, IRWWW | In vitro (HepG2 Cells) | Hypolipidemic activities through regulation of AMPK pathway | Hypocholesterolemic | Wang et al. 2020c |
| Soy protein hydrolysis | IAVPGEVA, IAVPTGVA, LPYP | In vitro (HepG2 cells) | Inhibited HMG-CoA reductase and modulated cholesterol metabolism | Hypocholesterolemic | Aiello et al. 2018 |
| Chickpea | VFVRN | In vivo (hyperlipidemic mice) | Decreased the levels of total cholesterol and total triglyceride in liver and serum, and increased the fecal triglyceride excretions | Hypocholesterolemic | Zhang et al. 2020b |

EITPEKNPQLR and RKQEEDEDEEQQRE, from soybean β-conglycinin inhibited FAS in vitro with $IC_{50}$ –values of 79, 27 and 16 µm, respectively (Martinez-Villaluenga et al. 2010). Similarly, peptides produced from altered β-conglycinin were reported to inhibit 50% FAS activity in vitro at a concentration of 50–175 µM, thus decreasing lipid accumulation (Mejia et al. 2010).

## Bioactive peptides in management of type-2 diabetes

Type-2 diabetes mellitus is a chronic condition that affects the glucose metabolism mechanism of the body. Type-2 diabetes arises due to body insulin resistance or low insulin production, which cannot maintain normal glucose levels (Bhardwaj et al. 2020). Type-2 diabetes is a multifaceted disease because it leads to several other complications like kidney failure, heart disease, blindness, and lower limb amputation (Jao et al. 2015). While several synthetic approaches (drugs) are available to manage blood sugar, they show many undesirable side effects including liver damage and high blood pressure. Henceforth, much attention is focusing on natural alternatives such as bioactive peptides for the management of type-2 diabetes. Dipeptidyl peptidase-IV (DPP-IV), α-amylase, and α-glucosidase are the key enzymes that have a direct role in the regulation of blood sugar, therefore peptides that inhibit activities of these enzymes are being developed as an effective strategy for the management of type-2 diabetes (Figure 2).

The key hormones responsible for regulation of insulin synthesis and secretion by the pancreas are the incretins, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). DPP-IV, an enzyme that is found both in the blood and in the cell membrane, is responsible for the inactivation of incretin hormones. The inhibition of DPP-IV in these circumstances can prolong the half-life of incretin hormones resulting in enhanced insulinotropic and glucoregulatory potentials (Nongonierma and FitzGerald 2015; Brandelli, Daroit, and Corrêa 2015; Zhu, He, and Hou 2019). DPP-IV inhibitory peptides have been identified from food proteins including casein, rice, soy and meat for the effective management of type 2 diabetes. Several reports suggest whey protein constituents such as leucine, isoleucine, valine, lysine, threonine are capable of elevating postprandial insulin requirement (Salehi et al. 2012). Previous reports suggested that dipeptides and tripeptides isolated from whey proteins may act as competitive inhibitors that prevent substrate access to DPP-IV active site, hence reduced catalysis (Gunnarsson et al. 2006; Zhu, He, and Hou 2019). Glycoproteins and lactoferrin whey proteins have documented activity on the action and signaling of insulin and insulin receptors. Nonetheless, several studies have linked insulin resistance to lactoferrin and other related disorders such as obesity and inflammation (Ayoub et al. 2018). Mortensen et al. (2012) reported that whey protein hydrolysate provoked insulin secretion from the isolated mouse Langerhans islets. Lacroix and Li-Chan (2014) identified 24 and 11 peptides from pepsin-treated whey protein, α-lactalbumin and β-lactoglobulin, respectively, showing in vitro DPP-IV inhibitory activity. Similarly, a β-lactoglobulin rich whey protein concentrate trypsin hydrolysate displayed prominent in vitro DPP-IV inhibitory activity (Silveira et al. 2013). Le Maux et al. (2015) also characterized a DPP-IV inhibitory activity of whey protein hydrolysate. Jia et al. (2020) recently, identified a potent DPP-IV inhibitory peptide (LDQWLCEKL) from α-lactalbumin with $IC_{50}$ value of 131 µm.

Furthermore, Ashok, Brijesha, and Aparna (2019) identified a heptapeptide (GIPLPLI) from fat globule membrane protein hydrolysates of buffalo colostrum, which inhibited in vitro activity of DPP-IV ($IC_{50}$ = 3.83 µm). Nongonierma et al. (2018) identified nine DPP-IV inhibitory peptides from trypsin hydrolysate of camel milk protein, among them LPVP (87 µm) and MPVQA (93.3 µm) had the lowest DPP-IV $IC_{50}$ value (strongest effect). Hu et al. (2019) identified a novel peptide (RSELAAWSR) from *Spirulina platensis*, which had DPP-IV $IC_{50}$ value of 167.3 µg/ml. Besides, two DPP-IV peptide (NAPNPR and YACSVR) has also been identified from *Sardine pilchardus* muscle (Rivero-Pino, Espejo-Carpio, and Guadix 2020). A novel peptide (LDKVFR) was reported from trypsin hydrolysate of salmon skin collagen with DPP-IV $IC_{50}$ value of 128.71 µm (Jin et al. 2020). Similarly, two peptides (LPIIDI and APGPAGP) were identified from Silver carp (*Hypophthalmichthys molitrix* Val.) protein hydrolysates exhibited strong competitive/non-competitive mixed-type inhibition against DPP-IV (Zhang et al. 2016).

Similarly, inhibition of α-amylase and α-glucosidase also lead to the reduction of dietary carbohydrates in blood. These enzymes are present on the cells that line the intestinal surface and are responsible for the conversion of complex sugars into monosaccharides, which are then absorbed. α-amylase, secreted from the salivary glands and the pancreas, causes an increase in blood glucose level by transforming dietary starch and glycogen into glucose and maltose. Similarly, α-glucosidase breaks down disaccharides into glucose in the small intestine to elevate blood glucose level (Yan et al. 2019). Ngoh and Gan (2018) identified five α-amylase inhibitory peptides from Pinto bean. Similarly, α-amylase inhibitory peptides were identified from Cumin seeds (Siow and Gan 2016; Siow, Lim, and Gan 2017). A novel peptide LPLLR was identified from walnut protein alcalase hydrolysates, with inhibitions of both α-glucosidase (50.12%) and α-amylase (39.08%) in vitro (Wang et al. 2020b). Mudgil et al. (2018) reported enhancement of α-amylase and DPP-IV inhibition in comparison of intact camel milk after enzymatic hydrolysis. Similarly, goat milk and kefir also displayed higher α-amylase inhibition after digestion (EI et al. 2015) (Table 1).

## Bioactive peptides in management of hypertension

Blood pressure is primarily regulated through the regulation of the renin-angiotensin system (RAS) by angiotensin converting enzyme (ACE), a nonspecific dipeptidyl carboxypeptidase. Renin, an aspartic protease cleaves angiotensinogen

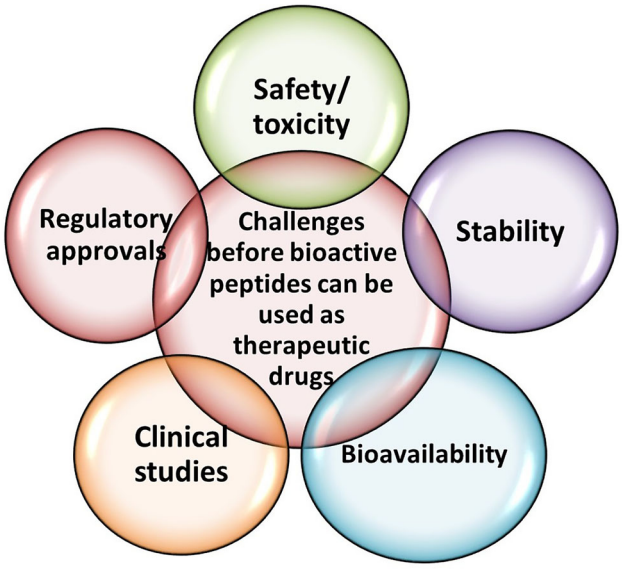


**Figure 3.** Schematic diagram of challenges ahead of therapeutic use and commercialization of bioactive peptides.

to form inactive angiotensin I decapeptide, which is then cleaved by ACE to release the octapeptide angiotensin II, a strong vasoconstrictor that controls blood pressure and certain hormones (Natesh et al. 2003; Singh, Vij, and Hati 2014; Martínez-Sánchez, Gabaldón-Hernández, and Montoro-García 2020; Singh, Bhushan, and Vij 2020). ACE also catalyzes bradykinin degradation in the kallikrein-kinin cycle, which is a blood pressure lowering nonapeptide (Cat and Touyz 2011). While synthetic ACE inhibitors have been shown to be quite effective in reducing blood pressure, there are safety issues that limit their utilization as therapeutic agents. Inhibiting the transformation of angiotensin I to angiotensin II by bioactive peptides can thus be a good alternative to synthetic drugs (Figure 2). These bioactive peptides are mainly considered competitive substrates for ACE and the C-terminal hydrophobic residues are the main factor in the process of binding (Martínez-Sánchez, Gabaldón-Hernández, and Montoro-García 2020). The sequence and length of peptides determine the receptor's affinity and the peptide's function because the ACE active site cannot bind large molecules and binding to ACE is strongly influenced by the peptide C terminal amino acid residues (Bouglé and Bouhallab 2017).

Among the bioactive peptides, ACE-inhibitory peptides have been studied extensively, with several peptides such as IPP, VPP, IPA, PP and GKP having an antihypertensive effect (Pan et al. 2011; Cicero et al. 2011). Antihypertensive peptides have been reported to be an effective therapy for mildly hypertensive patients, or even a supplemental medication (Espinosa-Hernández et al. 2019). A number of ACE-inhibitory peptides such as VPP and IPP were also produced by the action of proteolytic lactobacilli through fermentation (Solieri, Rutella, and Tagliazucchi 2015). In an animal study, a significant reduction in systolic blood pressure was observed when a spread containing bioactive milk peptides IPP and VPP was offered to hypertensive subjects (Turpeinen et al. 2009). Meta-analysis studies (Cicero et al. 2013; Cicero et al. 2011) have shown that milk-derived IPP and VPP peptides, which previously showed antihypertensive effect in Asian subjects, can also significantly decrease blood pressure in European subjects with 1.28 and 0.59 mmHg decreases in systolic (SBP) and diastolic (DBP) blood pressure (Table 2). Furthermore, a bioactive peptide sequence (RWDISQPY) has recently been identified in a brown seaweed *Sargassum maclurei,* which effectively lowers the systolic and diastolic blood pressure of spontaneously hypertensive rats (SHRs) at the concentration of 150 mg/kg body weight (Zheng, Zhang, and San 2020). Similarly, the antihypertensive effect of egg white peptides, QIGLF and RVPSL, has been documented in SHRs by 48 and 46 mmHg decreases, respectively in SBP (Yu et al. 2020). Two peptides, IQW and LKP, isolated from egg white, decreased mean blood pressure by ∼19 and ∼30 mmHg, respectively, when orally administered to SHRs (Majumder et al. 2015). A mushroom (*Tricholoma matsutakei*) derived peptide, WALKGYK, also significantly lowered the SBP of SHRs at the dosage of 25 mg/kg (Geng et al., 2016).

Additionally, LAFNPTQLEGQCHV, a peptide derived from sheep cheese whey $\beta$-lactoglobulin was reported to have inhibit about 55% of ACE activity in vitro (Corrêa et al. 2014). Some excellent ACE-inhibitory peptides (YLLK, YGIKVGYAIP, and LPWRPATNVF) have been detected from the protein of the palm kernel cake, showing 100% ACE inhibition in vitro (Zarei et al. 2015). Two novel peptides (IIY and PPL) have been identified with in vitro ACE-I inhibitory activities in porcine and bovine serum albumin (Lafarga, O'Connor, and Hayes 2014). Similarly, two novel peptides (KRQKYD and EKERERQ) that inhibit ACE-I have been identified by pepsin treatment from the porcine muscle (Katayama et al. 2008; Lafarga and Hayes 2014). Novel ACE inhibitory peptides, SAGGYIW and APATPSFW identified in wheat gluten using *Pseudomonas aeruginosa* protease hydrolysate showed $IC_{50}$ values of 0.002 mg/mL and 0.036 mg/mL, respectively in in vitro model (Zhang et al. 2020a). While angiotensin-converting enzyme (ACE) inhibition is considered a useful therapeutic method for treating hypertension, numerous animal and in vitro studies have indicated that mechanisms such as renin inhibition, nitric oxide-mediated vasodilation, and increased antioxidant response may also have effects on blood pressure (Singh, Vij, and Hati 2014; Martínez-Sánchez, Gabaldón-Hernández, and Montoro-García 2020) (Table 1).

## Bioactive peptides in management of hypercholesterolemia

Hypercholesterolemia is a metabolic condition characterized by elevated blood cholesterol levels, which has risen worldwide due to the incidence of high fat diets and non-healthy lifestyles (Prados, Marina, and García 2018). High levels of plasma cholesterol, particularly low-density lipoprotein (LDL) cholesterol, may cause arteriosclerosis by developing plaques in the arteries, with implication for cardiovascular disease outcome (Görgüç, Gençdağ, and Yılmaz 2020). The diet and biosynthesis of cholesterol, absorption and secretion

**Table 2.** Human studies on bioactive peptides identified from food proteins for the management of lifestyle-related diseases.

| Source of peptide | Peptide sequences | Study model | Result | Effect | Reference |
|---|---|---|---|---|---|
| Black soybean protein hydrolysates | NLQGENEEEDSGAIVTVK, VSIIDTNSLENQLDQMPR, KEQQQEQQQEEQPLEVR, EQQQEQQQEEQPLEVR, GNPDIEHPETM, LDTSNFNNQLDQTPRVF, NQEQEFLKYQ, RLLLLLGWLLIIVGVILLVGSTK, KEQQQEEQQEEQPLEVR, IIDTNSLENQLDQMPR, LDTSNFNNQLDQNPRVF, EQQQRQQQEEQPLE, PMDYYSDYDDNADDYFDDADDSDR | 34 overweight/obese subjects aged 19–65 years | Weight-lowering effects accompanied by favorable changes in metabolites in the subjects blood | Antiobesity | Kim et al. 2013 |
| Dairy protein | VPP, IPP | Meta-analysis of placebo-controlled clinical trials | Pooled effect of peptides was −5.13 mmHg for systolic blood pressure (SBP) and −2.42 mmHg diastolic blood pressure (DBP) | Antihypertensive | Pripp, 2008 |
| Dairy protein | VPP, IPP | Meta-analysis of clinical trials including 91 publications on the effect of IPP and VPP on SBP in Europeans | Decreases of SBP 1.28 mmHg and DBP 0.59 mmHg | Antihypertensive | Cicero et al. 2013 |
| Dairy protein | VPP, IPP | Meta-analysis of nine studies including 12 trials published between 1996 and 2005 with a total of 623 participants | Decreases of 4.8 mmHg in SBP and 2.2 mmHg in DBP | Antihypertensive | Xu et al. 2008 |
| Dairy protein | VPP, IPP | Randomized, double-blind, dose–response trial with 166 subjects | The effect on SBP/ DBP over 8 weeks compared with placebo was + 0.1/− 1.3, − 1.5/− 1.4 and − 2.5/− 1.9 mmHg for the low, medium and high dose of peptides, respectively | Antihypertensive | de Leeuw et al. 2009 |
| Sardine protein hydrolysates | VY | Randomized placebo-controlled trial with 63 subjects (male/female: 51/12) having mild hypertension. Dose level: 195 g (0.5 g VY) for 13 weeks. | 7.6 mmHg reduction in SBP and 4.5 mmHg reduction in DBP | Antihypertensive | Kawasaki et al. 2002; Iwaniak, Darewicz, and Minkiewicz 2018 |
| Soy protein hydrolysate | CSPHP | - | Reduction of cholesterol level in the plasma | Hypocholesterolemic | Ruiz, Ancona, and Campos 2014 |

affect plasma cholesterol levels. The hypocholesterolemic effect of bioactive peptides has been reported in several studies such as lactostatin (IIAEK), a cow's milk derived peptides documented hypocholesterolemic activity in HepG2 human liver cell line., which was higher than a known anti-hypercholesterolemic drug "sitosterol" (Morikawa et al. 2007). Existing data suggest that hypocholesteromic peptides target exogenous cholesterol by impeding the absorption of dietary cholesterol. Instead, cholesterol metabolism pathways are targeted for the management of endogenous cholesterol levels. Some peptides prevent bile acid distribution while others specifically target the metabolism of endogenous cholesterol in tissues. Hypocholesteromic effect of bioactive peptides has also been recognized through the inhibition of HMG-CoA reductase, the key enzyme for cholesterol synthesis (Boachie, Yao, and Udenigwe 2018) (Figure 2).

Ten lipid-lowering peptides from olive seed proteins were identified by Prados, Marina, and García (2018), with activities demonstrated through various pathways, including in vitro decreasing the solubility of micellar cholesterols, the inhibition of cholesterol esterase and lipase enzymes. Jiang et al. (2020) found the hypocholesterolemic effect of milk-derived peptides, TDVEN, LQPE, VAPFPE, and VLPVPQ through reduction in the solubility of micellar cholesterol in vitro. Among them VLPVPQ significantly decreased mRNA expression of acetyl-CoA-acetyltransferase 2 in caco-2 cell model, which plays a major role in facilitating cholesterol absorption. Marques et al. (2015) identified hypocholesterolemic peptide (GCTLN) from cowpea bean proteins which inhibited HMG-CoA reductase enzyme in vitro. Furthermore, Marques et al. (2018) reported that cowpea hydrolysate interferes with the absorption of intestinal cholesterol and inhibits expression of Niemann-pick C1-like 1 (NPC1L1) protein, which is responsible for intestinal cholesterol uptake. e Silva et al. (2018) reported HMG-CoA reductase inhibitory activity ($IC_{50} = 12.8$ μM) of tripeptide QDF isolated from cowpea $\beta$-vicilin protein. Two pentapeptides, VIAPW and IRWWW, isolated from *Miichthys miiuy* muscle, significantly inhibited lipid accumulation and decreased intracellular levels of intracellular triglyceride (TG) and total cholesterol (TC) in HepG2 cells (Wang et al. 2020c). Prados et al. (2020) recently found concentration-dependent inhibition of HMG-CoA reductase by olive seed peptides. Also, the higher concentration of olive seed hydrolysate showed 25% reduction in total cholesterol in male mice after 11 weeks. Wan et al. (2020) found bile acid binding capability of *Trachinotus ovatus* muscle proteins trypsin hydrolysates using a mice model. Recently, Zhang et al. (2020b) reported a substantial decrease in total cholesterol and total triglyceride levels in liver and serum, and an increased in the fecal excretion of triglycerides in hyperlipidemic mice model after administration of VFVRN, a chickpea peptide (Table 1).

## Future research perspective

There are several challenges before bioactive peptides can be commercialized and used as therapeutic drugs or functional foods (Figure 3). Bioactive peptides are presently being tested for the management of lifestyle diseases, but efficacy of peptides is always a concern due to their extensive hydrolysis during processing conditions and by proteolytic enzymes of the digestive tract. Processing conditions like temperature, and length of fermentation or hydrolysis, can result in the generation of non-reproducible peptides, particularly when a protein mixture is present in the substrate. It has been observed that processing may be detrimental to some peptides, but improve the activity of other bioactive peptides. Some undesirable substances with toxic, allergenic, or carcinogenic properties may be generated in foods by the reaction of bioactive peptides with other constituents like carbohydrates and lipids (Daliri, Lee, and Oh 2018b). Although bioactive peptides are derived from food proteins, they are prepared using microbial proteases, some of which have not been scientifically proven to be safe (Liu et al. 2020). Thus, in order to produce foods with particular health effects, the optimal conditions must be investigated and applied. Moreover, bioactive peptides that have been shown to be beneficial at an appropriate dose may have harmful effects if they are ingested at higher or longer-term levels. Generally, bioactive peptides are considered safe, but treatments which degrade the quality and safety of peptides need to be avoided.

A burgeoning body of literature has appeared in recent decades on the functional activities of bioactive peptides, especially in vitro data. But in vitro efficacy of bioactive peptides may not always correlate with in vivo effect, as they are likely to be impaired in the intestine, vascular system, and liver. Preliminary pharmacokinetic studies are, therefore, necessary before human interventional trials are performed. Bioactive peptides must remain active during digestion by human proteases and be transferred into the blood through the intestinal wall for maximum effect. In order to effect the transport and bioavailability of intact peptides, structural properties such as hydrophobicity, charge, peptide sequence, and low molecular size are important factors (Sun et al. 2020). Small peptides are more readily absorbed than large peptides as they easily cross the intestinal barrier and exert their function at the tissue level. It was shown that a minimum concentration of bioactive peptides is required to exercise a particular role at the tissue level once they pass through the intestinal barrier (Gardner 1988).

While a range of peptide absorption pathways are studied, such as paracellular, PepT1-mediated permeation, passive diffusion, carrier transport, endocytosis, and lymphatic system, but they are not inclusive as their rationally intended drug counterparts (Sarmadi and Ismail 2010; Sun et al. 2020). This knowledge is crucial for understanding transportation pathways and the bioavailability of peptides and therefore needs to be incorporated into future work. Low bioavailability can significantly hinder use of bioactive peptides in developing functional foods and nutraceutical products. Hence, knowledge of bioactive peptide stability in the gastrointestinal tract and site-specific delivery at target locations in the body should be improved in future research

activities. Nanoparticles or nanoconjugates can be developed in this direction to encapsulate, stabilize and deliver bioactive peptides. Food-grade carriers may be appropriate for use in functional foods, but they should have no peptide reactivity. A wide range of colloidal systems has been recommended such as chitosan nanoparticles, nanoliposomes and biopolymer based microgels (McClements 2018; Sun et al. 2020). Hence, extensive studies that show significant evidence of improving bioavailability of bioactive peptides upon encapsulation are required.

Another aspect that should be a focus of research activities is the clinical studies on bioactive peptides. Many potential food bioactive peptides have been documented over the years, but barriers such as the absence of well-designed clinical trials to provide robust evidence that prove health claims continue to exist. However, a few clinical trials have demonstrated antihypertensive and lipid-lowering activities of bioactive peptides extracted from fish, milk, meat and plants. Many bioactive peptides, on the other hand, exhibit selective cytotoxicity against a broad range of cancer cell lines but without clinical evidence of anti-cancer efficacy (Cicero, Fogacci, and Colletti 2017).

Another important factor is regulatory approvals, which protects customers from risks, deceptive and fraudulent statements regarding efficacy and use of bioactive peptides. In vitro and animal experiments are not sufficient to argue that bioactive peptides have a beneficial impact, but must be backed by significant evidence from human studies. There are currently a number of regulatory criteria for the authorization of bioactive peptides in various countries. For instance, the American Diabetes Association and the European Association for the Study of Diabetes have suggested that α-amylase and α-glucosidase inhibitors be used in conjunction with other anti-hyperglycaemic drugs or as a possible first-line agent (Yan et al. 2019). While, as of now, hundreds of bioactive peptides have been identified from several sources of food protein, only a few are marketed as functional foods (Chalamaiah et al. 2019). In order to validate functional effects, more animal experiments and randomized human intervention trials are needed, in order to allow the use of bioactive peptides as preventive or therapeutic treatments.

## Conclusion

Food-derived bioactive peptides have potential to be used as therapeutic drug or functional food supplement to treat lifestyle-related diseases. Scientific research is underway to discover novel peptides from different sources of food proteins. New targets are being investigated to assess the effectiveness of peptides. Along with technological advancement in the peptide discoveries, more alternate pathways should be identified to target complications especially obesity and type 2 diabetes. There is less available data on in vivo and clinical trials compared to in vitro studies, so this field needs to be targeted. Moreover, the strategy for stability and target delivery of peptide by applying micro- and nano-conjugation need to be focused. Besides, for productive sequences, clinical trials need to be performed and regulatory criteria should concentrate on the purpose of commercialization.

## Conflict of interest

No conflict of interest declared.

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