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Review

Roles of exogenous bioactive peptides in obesity and obesity-related diseases: A review

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Abstract

Exogenous bioactive peptides (eBAPs) are short amino acid peptides that are released through enzymatic hydrolysis. These peptides are derived from various sources such as oysters, soybeans, eggs, and other foods. The eBAPs exhibit a range of biological activities. Recent studies have shown that eBAPs have the potential to alleviate and mitigate obesity and its associated metabolic disorders. These disorders include cardiovascular diseases, hypertension, insulin resistance, and type 2 diabetes. In the present review, we have summarised the biological activities and production of eBAPs and their physiological regulatory functions in relation to obesity and obesity-related diseases. These findings would provide new insights and encourage further in-depth research on eBAPs.

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Introduction

Obesity has emerged as a significant global public health challenge, affecting both developed and developing nations due to economic growth and lifestyle changes (Lee and Yoon, 2018; von Heesen, 2022; Mathis *et al*., 2023). Characterised by excessive accumulation of white adipose tissue, obesity disrupts energy balance, and is a major risk factor for chronic diseases such as type 2 diabetes, cardiovascular diseases (CVD), hypertension, and certain cancers (Koliaki *et al*., 2019; Haidar and Horwich, 2023; Mallah *et al*., 2023). The pro-inflammatory and pro-thrombotic environments induced by obesity exacerbate these conditions, highlighting the urgent need for effective interventions (Mathew *et al*., 2008; Tian *et al*., 2022).

Food proteins play a crucial role as a source of energy and amino acids, supporting normal growth, life maintenance, and reproduction (Markoulli *et al*., 2023). Apart from their nutritional value, food proteins can also be digested by proteases to generate peptides with specific biological activities, known as bioactive peptides (Sotoudeh and Azizi, 2023; Oliveira *et al*., 2024; Yuan *et al*., 2024; Moreira *et al*., 2024). At present, although many reviews on bioactive peptides have been published, the systematic and comprehensive review on exogenous bioactive peptides (eBAPs) remain scarce. While bioactive peptides have been extensively reviewed for their metabolic benefits, eBAPs represent a distinct and emerging subfield. Moreover, the mechanisms by which eBAPs reduce fat deposition, improve metabolic health, and alleviate obesity-related diseases remain insufficiently understood. Additionally, challenges such as peptide stability, bioavailability, and clinical efficacy limit their widespread application (Patil *et al*., 2022; Ejike *et al*., 2023). Therefore, the present review aimed to (1) summarise the biological activities and physiological regulatory functions of eBAPs in obesity and related metabolic disorders; (2) evaluate the mechanisms through which eBAPs exert their beneficial effects, including modulation of lipid metabolism, hypertension, and insulin signalling; and (3) identify gaps in current research and propose future directions for the development of eBAP-based interventions.

To develop the present review, established scientific databases such as Scopus, PubMed, and Web of Science were searched using the following keywords: 'food proteins', 'bioactive peptides', 'exogenous bioactive peptides', 'obesity', 'adipose',

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'disease', 'cardiovascular disease', 'hypertension', and 'type 2 diabetes'. The present review then only included articles published in English language, with most of them being published over the last five years.

Comparison between endogenous BAPs and exogenous BAPs (eBAPs)

Bioactive peptides are easily digested and absorbed by the body, and have been found to play roles in boosting immunity, regulating hormone secretion, reducing blood pressure, and lowering lipid levels (Patil *et al*., 2022; Acevedo-Juárez *et al*., 2022). Bioactive peptides can be broadly categorised into two groups: endogenous and exogenous bioactive peptides (Yoshikawa, 2015; Dave *et al*., 2021; Tanikawa *et al*., 2021). Endogenous bioactive peptides are naturally released from precursor proteins and secreted by cells. Whereas, exogenous bioactive peptides (eBAPs) are derived through industrial processes or are small molecular peptides that are digested from protein hydrolysate by endogenous intestinal enzymes (Abeer *et al*., 2021). More precisely, endogenous bioactive peptides can be defined as peptides produced from the human proteome inside the “body proper”, that may either play a role in physiological regulation or exert a health benefit (Karelin *et al*., 1998), while eBAPs are generated outside the “body proper” (Dave *et al*., 2016).

The production of eBAPs from various biological sources follows fundamentally similar approaches, with three primary methodologies being predominantly utilised: enzymatic hydrolysis, chemical hydrolysis, and microbial fermentation. Since most bioactive peptides are buried or encrypted in the structure of mature proteins, the most common and simple method for producing bioactive peptides is enzymatic hydrolysis, especially by digestive enzymes (Zambrowicz *et al*., 2013). Enzymatic hydrolysis is the most favourable peptide production approach due to its several advantages compared to the other methods, such as high specificity, mild conditions, lack of residual organic solvents and toxic chemicals in the final peptide preparations, along with the fact that food-grade enzymes-derived bioactive peptides are commonly recognised as GRAS (Generally Recognised as Safe) (Wang *et al*., 2017; Ulug *et al*., 2021; Sridhar *et al*., 2021; Cunha and Pintado, 2022). The use of gastrointestinal enzymes to produce bioactive peptides makes it possible to administer the resulting peptides orally (Räder *et al*., 2018). Nevertheless, enzymatic hydrolysis has some drawbacks, including high cost of enzymes, enzyme cleavage site specificity, control of pH and temperature parameters to achieve optimum hydrolysis, and low yield of final product. Hence, there has been a need for alternative methods (Tadesse and Emire, 2020). Conventionally, bioactive peptides are produced from different food sources (milk, egg, meat, marine sources, and plant) by enzymatic hydrolysis and/or microbial fermentation technologies (Cruz-Casas *et al*., 2021) and/or simulated gastrointestinal digestion procedures. Plant-based meat eBAPs are obtained by simulating gastrointestinal digestion, and then hydrolysis with pepsin and pancreatin (Wang *et al*., 2023a). Current industrial production of eBAPs predominantly relies on three conventional proteolytic enzymes (pepsin, trypsin, and papain), which exhibit limited substrate specificity and suboptimal yield efficiency. To address these limitations, the development of customised hydrolytic enzymes designed for specific peptide sequences represents a critical research direction. Strategic optimisation of enzyme-substrate combinations based on structural characteristics would significantly improve both the production yield and bioactive quality of eBAPs, thereby enhancing their commercial viability and therapeutic applications.

Chemical hydrolysis of proteins is the oldest process for the generation of food-derived biologically active peptides that involves the use of acid or alkali to cleave the peptide bonds allowing the release of peptides and free amino acids. Chemical hydrolysis breaks down proteins using acids like hydrochloric acid (Ashaolu, 2020) or bases such as calcium, sodium, or potassium hydroxide (Alvarez-Vinas *et al.*, 2021). Despite being cost-effective and rapid, chemical hydrolysis lacks precise control over hydrolysate consistency, and leads to variations in amino acid profiles due to non-specific hydrolysis (Siddik *et al.*, 2021). Although chemical hydrolysis is widely used as a conventional technology, being simple with low costs, it has several limitations, including variable chemical compositions production due to difficulties in process controlling. Besides, the use of harsh chemicals and solvents under extreme temperature and pH conditions often results in poor nutritional qualities and low functionalities, as well as environment pollution (Ulug *et al*., 2021). Microbial fermentation is another approach to producing

biologically active peptides from different sources that is becoming attractive due to its GRAS status (devoid of any pathogenicity and toxicity in humans) and its relatively low cost compared to enzymatic technology (Tasdemir and Sanlier, 2020; Dominguez-Perez *et al*., 2020). Low peptide yield and a lack of specificity in peptide formation are the major disadvantages that impede microbial fermentation from being industrially exploited for the generation of peptides/protein hydrolysates endowed with health-related benefits purposes (Manzoor *et al*., 2022). Current eBAP manufacturing continues to rely predominantly on conventional production methods (enzymatic/chemical hydrolysis and microbial fermentation), highlighting a substantial innovation deficit in this field. While these methodological constraints reflect the inherent complexity of bioactive peptide production, they simultaneously underscore untapped opportunities for technological breakthroughs. The development of next-generation production platforms could fundamentally transform manufacturing paradigms by simultaneously enhancing production yields, product quality consistency, and application scope, thereby unlocking unprecedented commercial and therapeutic value.

eBAPs and obesity

Obesity is characterised by pathological changes in adipose tissue, which result in a state of low-grade chronic inflammation throughout the body. These changes include the abnormal accumulation of pro-inflammatory white blood cells within adipose tissue (El Meouchy *et al*., 2022). Adipose tissue is not just a passive storage site for fat; it is a dynamic and metabolically active endocrine organ (Karakurt and Pir, 2023; Monsalve *et al*., 2023; Nikiforaki and Marias, 2023). It plays a crucial role in storing and releasing fatty acids and producing adipokines, which are important in regulating energy balance and glucose metabolism (Suryaningtyas and Je, 2023; Banfi *et al*., 2023). Research has indicated that when used as functional food ingredients, eBAPs do not accumulate in body tissues (Lordan *et al*., 2011). These bioactive peptides can have local effects in the gut by interacting with specific receptors or cells, or they can pass through the intestinal epithelium and enter the bloodstream, adsorbed by target tissues or organs, leading to systemic effects *in vivo* (Miner-Williams *et al*., 2014; Matsui, 2018; Xu *et al*., 2019; Amigo and Hernandez-Ledesma, 2020). In recent years, there has been a growing interest in using eBAPs as both a source of nutrition and therapeutic agents (Wang *et al*., 2023b; Ma *et al*., 2023; Suryaningtyas and Je, 2023). These peptides have the potential to be used as food additives or nutritional supplements to alleviate and mitigate various chronic diseases in humans. Currently, there are several natural eBAPs that are being tested or have already entered the market as dietary supplements or health foods (Patil *et al*., 2022).

Comparing the different mechanisms of action of eBAPs can provide valuable insights into their potential role in preventing and treating obesity and its associated metabolic changes (Hu *et al*., 2023; Koirala *et al*., 2023; Liu *et al*., 2023a; Wang *et al*., 2023b). To facilitate this comparison, Table 1 summarises the preparation methods, bioactive components, animal (cell) models used in the past three years, and the mechanisms of action for preventing obesity.

Animal-derived eBAPs and obesity

This comprehensive overview will help in understanding the diverse approaches and potential benefits of eBAPs in combating obesity (Mellinkoff *et al*., 1956; Froetschel *et al*., 2001; Nongonierma *et al*., 2013; Mitkin *et al*., 2022). Indeed, eBAPs derived from milk or dairy products have shown potential in controlling body weight and obesity (Delgadillo-Puga *et al*., 2020; Öztürk *et al*., 2022; Koirala *et al*., 2023; Suryaningtyas and Je, 2023). One specific example is the milk hydrolytic peptide CHM-273S (Mitkin *et al*., 2022; Pavshintsev *et al*., 2022), as listed in Table 1. This peptide has demonstrated a prominent anorexigenic effect in mice by inducing the key mechanism of leptin signalling *via* STAT3 in the hypothalamus, as shown in Figure 1. The results of the study are indeed intriguing. Mice treated with chronic administration of the milk hydrolytic peptide CHM-273S exhibited significant weight loss, reduced visceral fat pad weight, and a decrease in size of fat cells. Notably, the effectiveness of CHM-273S was found to be comparable to that of strychnine, a known appetite suppressant (Mitkin *et al*., 2022). Nevertheless, the putative role of eBAP-modulated leptin signalling pathways in mediating the observed anti-obesity effects warrants systematic investigation. The current evidence base remains limited by: (i) a paucity of mechanistic *in vitro* studies characterising

Table 1. Summary on roles and mechanisms of eBAPs in preventing obesity.

Source	Preparation method	Bioactive component	Model	Action mechanism
Ruditapes philippinarum (Song *et al*., 2022)	*Philippinarum* and sucrose by *Bacillus natto* for 24 h at 45°C	Fermentation mixture	Kunming mice	By upregulating the liver expression of genes associated with lipolysis.
Corn (Zhang *et al*., 2022; Wei *et al*., 2022)	Commercial purchase	Corn bioactive peptides	Sprague Dawley rats, LO2, 3T3-L1 cells	Increased the expression of SIRT2/PPAR-α and Nrf1/HO-2 pathways in LO2 cells, and inhibited the expression of key adipogenesis regulators C/EBPα, C/EBPβ, PPARγ, and FABP4.
Spinach (Kaneko *et al*., 2022)	Pepsin-trypsin	YHIEPV	Male C57BL/6 and ddY mice	Blocked Epac-Rap1 signalling pathway and decreased the level of brain Rap1 in GTP-bound active type.
Cattle (Mitkin *et al*., 2022)	HPLC/MS-MS	CHM-273S peptides from milk hydrolysate	Primary murine fibroblasts, male C57BL/6 mice, and male Sprague Dawley rats	STAT3 in the hypothalamus as a key mechanism for possible effector-induced leptin signalling. Induced Akt Ser473 and Thr308 phosphorylated.
Jellyfish *Nemopilema nomurai* (Ma *et al*., 2023)	Papain	Enzymatic hydrolysate	3T3-L1 preadipocytes	Induced synergistic remodelling of the metabolic network of 3T3-L1 cells to prevent lipid accumulation and inhibited adipogenesis by downregulating energy metabolism.
Vitalmelon (Guo *et al*., 2022)	Freeze-dried vitalmelon fruits were ground to a powder and passed through a 30-mesh sieve.	Edible vitalmelon fruit extract	3T3-L1 preadipocytes	Down-regulated of PPARγ and PPARγ-target genes LPL, CD36, HMGCR, and L-FABP, and inhibited the differentiation of 3T3-L1 preadipocytes.

SIRT2: Sirtuin 2; PPAR-α: peroxisome proliferators-activated receptor α; Nrf1: nuclear respiratory factor-1; HO-2: Heme oxygenase-2; LO1: human non-tumour hepatic cells; C/EBPα: recombinant human CCAAT/enhancer binding protein alpha; C/EBPβ: CCAAT enhancer binding protein beta; PPARγ: peroxisome proliferator-activated receptor gamma; FABP4: fatty acid binding protein 4; Rap1: Ras-proximate-1; STAT3: signal transducer and activator of transcription 3; LPL: lipoprotein lipase; CD36: platelet glycoprotein 4; HMGCR: 3-hy-droxy-3-methyl glutaryl coenzyme A reductase; and L-FABP: liver fatty acid binding protein.

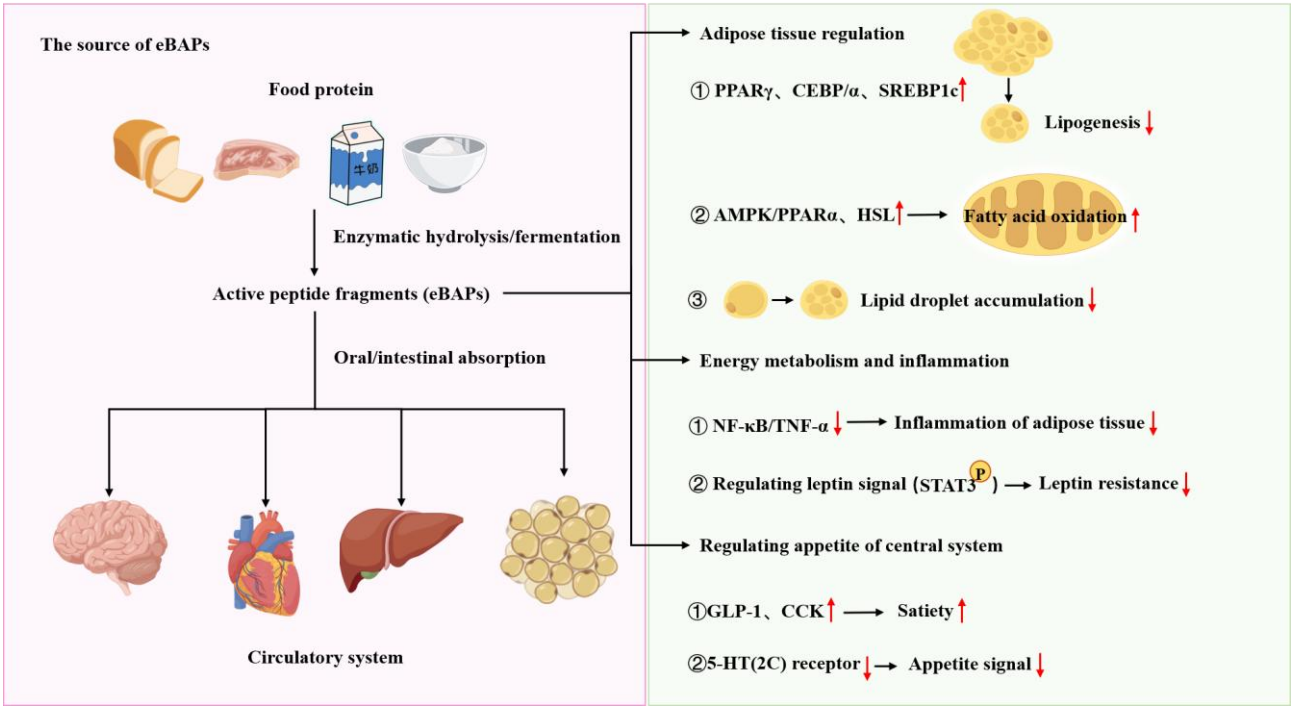

Figure 1. Mechanism of eBAP intervention on obesity.

cellular responses, and (ii) insufficient *in vivo* validation across relevant animal models. These knowledge gaps preclude definitive elucidation of: (a) the precise molecular mechanisms underlying eBAPs' anti-adipogenic actions, and (b) their regulatory effects on lipid homeostasis genes (particularly the coordinated modulation of both lipogenic [*e.g.*, SREBP-1c and FAS] and lipolytic [*e.g.*, ATGL and HSL] targets). Additionally, eBAPs derived from casein, as listed in Table 1, has been shown to induce satiety through different mechanisms. One such mechanism involves stimulating the release of cholecystokinin (Froetschel *et al*., 2001) (CCK) and glucagon-like peptide-1 (Jakubowicz and Froy, 2013) (GLP-1). GLP-1 is known to play a crucial role in energy balance, regulating blood sugar levels through its proliferative action, and promoting satiety while reducing food intake through its anorexic properties (Chang *et al*., 2019). Furthermore, the stimulation of serotonin receptors by casein eBAP indicates a potential for suppressing appetite (Nongonierma *et al*., 2013). When the concentration of amino acids increased and blood sugar levels decreased, the administration of casein eBAP, whether intravenous or oral, resulted in a reduction in appetite (Mellinkoff *et al*., 1956). Currently, research on casein eBAP has focused on its potential to reduce fat deposition and chronic fat inflammation (Liu *et al*., 2023a). However, the specific mechanism underlying these effects is still under investigation (Ejike *et al*., 2023).

A variety of marine eBAPs showed an inhibitory effect on obesity (Song *et al*., 2022; Ma *et al*., 2023). *Ruditapes philippinarum* eBAPs, as listed in Table 1, significantly reduced body weight, adipose tissue weight, lipid accumulation in the liver, and plasma total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL) levels in mice. Mechanism analysis has shown that *Ruditapes philippinarum* eBAPs up-regulated the liver lipolysis-related genes, such as hormone-sensitive lipase, PPARα, and phosphorylated AMP-activated protein kinase (p-AMPK), and down-regulated the lipid synthesis gene, PPARγ. In addition, *Ruditapes philippinarum* eBAPs reduced obesity and hyperlipidaemia by regulating the disordered composition of intestinal microbiota, increasing the microbiota abundance associated with the synthesis of short-chain fatty acids, controlling the microbiota associated with intestinal inflammation, and exerting weight loss and lipid-lowering activities (Song *et al*., 2022). The eBAPs from jellyfish *Nemopilema nomurai*, as listed in Table 1, down-regulated glycerolipids, and up-regulated sphingolipid metabolism and sphingolipid signalling pathways. In addition, ATP levels in the tricarboxylic acid cycle and oxidative phosphorylation pathways were significantly reduced, which was associated with

glucagon signalling pathways and fatty acid synthesis. To date, research has merely demonstrated correlative associations between eBAP administration and metabolic improvements, while failing to mechanistically characterise their interactions with critical pathway components at both genomic and proteomic levels. This fundamental gap in mechanistic understanding substantially impedes our ability to decipher eBAPs' mode of action and therapeutic potential. The lipid-lowering activity of pickled jellyfish *Nemopilema nomurai* eBAPs might be related to lipid and energy metabolism in 3T3-T1 cells; ATP might be a potential lipid-lowering biomarker with a change factor of 0.534 (Ma *et al*., 2023). eBAPs exhibit considerable therapeutic promise for obesity management due to their capacity to simultaneously modulate multiple pathological pathways underlying obesity. To advance this field, future investigations should prioritise: (1) establishing robust lipidomic biomarkers that can serve as sensitive indicators of metabolic response, and (2) developing analytical frameworks that integrate these biomarkers to elucidate eBAP-mediated regulation of lipid homeostasis at molecular levels.

Plant-derived eBAPs and obesity

Some familiar crop sources of eBAPs also have fat-reducing effects (Tsou *et al*., 2013; Peighambardoust *et al*., 2021; Nagaoka *et al*., 2021; Kaneko *et al*., 2022; Zhang *et al*., 2022; Wei *et al*., 2022; Wu *et al*., 2022; Yi *et al*., 2023). Previous studies in our laboratory showed that corn peptides (CPs), as listed in Table 1, inhibited the adipose differentiation and lipid accumulation of 3T3-L1 preadipocytes. Oral CPs decreased serum TG content, epididymal fat weight, abnormal hepatic fat drop accumulation, and CCAAT/enhancer-binding protein α (C/EBPα) expression. Serum levels of total cholesterol (TC), TG, and LDL were decreased, and liver lipid droplet accumulation and epididymal adipocyte hypertrophy were inhibited. Additionally, this combination inhibited the expression of transcription factors, C/EBPα, C/EBPβ, and PPARγ, and adipogenic factor FABP4 in mice (Zhang *et al*., 2022). Recently, another *in vivo* study on corn peptides (Wei *et al*., 2022) showed that CPs could effectively reduce the rate of weight gain, lipid levels, and liver index, and increase glucose tolerance. The results of *in vitro* experiments showed that CPs could effectively reduce the accumulation of lipids in LO2 cells, inhibit the accumulation of reactive oxygen species (ROS), and significantly reduce the accumulation of liver lipids *in vitro* and *in vivo.* CPs also decreased the sterol regulatory element binding protein-1c (SREBP1c) expression in LO2 cells.

Meanwhile, the expression of SIRT1/PPARα and Nrf2/HO-1 pathways increased in LO2 cells after pre-treatment with CPs, indicating that CPs could significantly reduce fatty liver injury induced by high fat, regulate insulin sensitivity, and reduce the production of ROS (Wei *et al*., 2022). The lipid-modulating efficacy of eBAPs exhibits substantial source- and dose-dependent variability, necessitating systematic evaluation of the potential safety implications associated with these pharmacological inconsistencies. LC-MS/MS analysis of soybean hydrolysate identified three lipopolysaccharide-stimulating peptides (Tsou *et al*., 2013) (ILL, LLL, and VHVV), which might enhance the stimulating effect of lipopolysaccharide, and would not be affected by gastrointestinal protease activity. Importantly, these peptides possess lipolysis-stimulating activity (Tsou *et al*., 2013). While *in vitro* analyses have demonstrated that pepsin-mediated proteolysis preserved the lipolytic function of these three eBAPs, their biological efficacy under physiological conditions requires further validation through rigorous *in vivo* studies.

Studies have demonstrated that soybean eBAPs exhibited inhibitory effects on metabolic regulation and physiological properties (Nagaoka *et al*., 2021; Peighambardoust *et al*., 2021; Kaneko *et al*., 2022). These effects include reducing cholesterol and triglyceride levels, improving lipid metabolism, combating obesity, inhibiting fatty acid synthase (FAS), and exerting anti-diabetic effects (Nagaoka *et al*., 2021). Additionally, soybean eBAPs have been found to be more effective than proteins in reducing total blood cholesterol levels (Peighambardoust *et al*., 2021). The underlying mechanism of this phenomenon, specifically whether it derives from eBAPs' intrinsic structural specificity or is mediated by matrix-related effects, requires systematic investigation through well-controlled experimental approaches. YHIEPV, an active peptide derived from spinach eBAPs, as listed in Table 1, demonstrated its ability to enhance the phosphorylation of STAT3 in hypothalamic slice cultures *in vitro*, which is induced by leptin. Furthermore, YHIEPV was found to alleviate the decrease in leptin responsiveness caused by palmitic acid. In obese mice, YHIEPV restored

cellular leptin sensitivity and the levels of pro-inflammatory-related factors, including *IL1β* and *Socs-3*, in the hypothalamus. YHIEPV was found to counteract cellular leptin resistance caused by forskolin, which activates Epac-Rap1 signalling. Additionally, YHIEPV decreased the level of the active GTP-bound form of Rap1 in the brains of obese mice. This peptide also enhanced neural leptin responsiveness, and reduced body weight gain in mice with dietary obesity (Kaneko *et al*., 2022). YHIEPV demonstrates pleiotropic regulatory effects across multiple metabolic pathways; however, its precise mechanisms of action remain inadequately characterised at both the cellular and organismal levels. Although accumulating evidence supports the therapeutic promise of eBAPs for obesity management, their modes of action diverge fundamentally from conventional pharmacological interventions. To advance this field, future investigations should integrate multi-omics approaches (including proteomic, metabolomic, and transcriptomic analyses) to comprehensively delineate the molecular networks through which eBAPs exert their anti-obesity effects, thereby enabling the rational design of targeted therapies for obesity and its metabolic comorbidities.

Roles of eBAPs in obesity-related diseases

eBAPs and cardiovascular disease

Cardiovascular disease (CVD) encompass a range of heart and blood vessel conditions, including deep vein thrombosis, pulmonary embolism, stroke, ischemic heart disease (Yang *et al*., 2017; Rafiq *et al*., 2017). These diseases pose a significant global public health challenge, and are often caused by varying levels of blood clotting in the blood vessels (Zhou *et al*., 2022; Goldsborough *et al*., 2022; Chandika *et al*., 2022). As a result, there is an increasing need for research and development of foods that contain anticoagulants and antithrombotic agents. In addition to preventive and therapeutic drugs, there has been a growing emphasis on dietary eBAPs in promoting cardiovascular health (Cermeño *et al*., 2019; Rengasamy *et al*., 2019; Chernukha *et al*., 2021; Ejike *et al*., 2023). Among these natural peptides, hirudin is known for its potent thrombin inhibitory activity (Cheng *et al*., 2021). However, it is also associated with several side effects, including allergies, bleeding, and poisoning, as it is derived from the saliva or venom of blood-eating animals (Cheng *et al*., 2021). Therefore, it is crucial to explore new anticoagulants with minimal side effects for the prevention of thromboembolism.

A newly discovered anticoagulant eBAP (Cheng *et al*., 2018), TARNEANVNIY, has been isolated, purified, and identified from oysters. This eBAP effectively prolongs the activated partial thromboplastin time (aPTT) and the prothrombin time (PT). Its amino acid sequence bears resemblance to the C-terminal fragment (DFEEIPEEYLQ) of hirudin, a highly efficient thrombin inhibitor previously mentioned. The oyster-derived eBAP TARNEANVNIY specifically inhibits the activity of thrombin (Cheng *et al*., 2018) as shown in Figure 2, and effectively reduces the occurrence of CVD. Recently, another novel anticoagulant heptapeptide (Cheng *et al*., 2021), P-3-CG, has been isolated from the pepsin hydrolysate of oysters. P-3-CG competes with fibrinogen for the antithrombin active domain through a spontaneous exothermic reaction driven by entropy. The Lys7 residue of P-3-CG strongly anchors the thrombin S1 bag, inhibiting the binding of fibrinogen to thrombin, and blocking the conversion of fibrinogen to fibrin. This leads to an extended fibrinogen coagulation time of 27.55 seconds. The enzymolysis activity of thrombin is significantly influenced by the reaction time and concentration of P-3-CG. Additionally, P-3-CG significantly prolongs the *in vitro* and *in vivo* activated aPTT (Cheng *et al*., 2021), as shown in Figure 2. These findings suggest that P-3-CG, as an alternative food-derived anticoagulant peptide, could be utilised for thrombosis prevention.

The potential applications of scorpion eBAPs in functional foods and anticoagulant drugs are significant, as they can help maintain blood flow, and prevent atherosclerosis (Ren *et al*., 2014). Potato eBAPs have been found to protect heart tissue by activating autophagy and mitochondrial biogenesis pathways, which in turn alleviates cardiac cell apoptosis in spontaneously hypertensive rat models (Lin *et al*., 2020). Soy eBAPs, on the other hand, effectively reduced blood cholesterol levels and LDL, as well as lipid accumulation, by regulating bile acid reabsorption in the digestive system or organs. This makes soy eBAPs a promising option for the prevention and treatment of atherosclerosis (Caponio *et al*., 2021). Future investigations should employ integrated approaches to systematically elucidate: (1) the precise molecular mechanisms through which

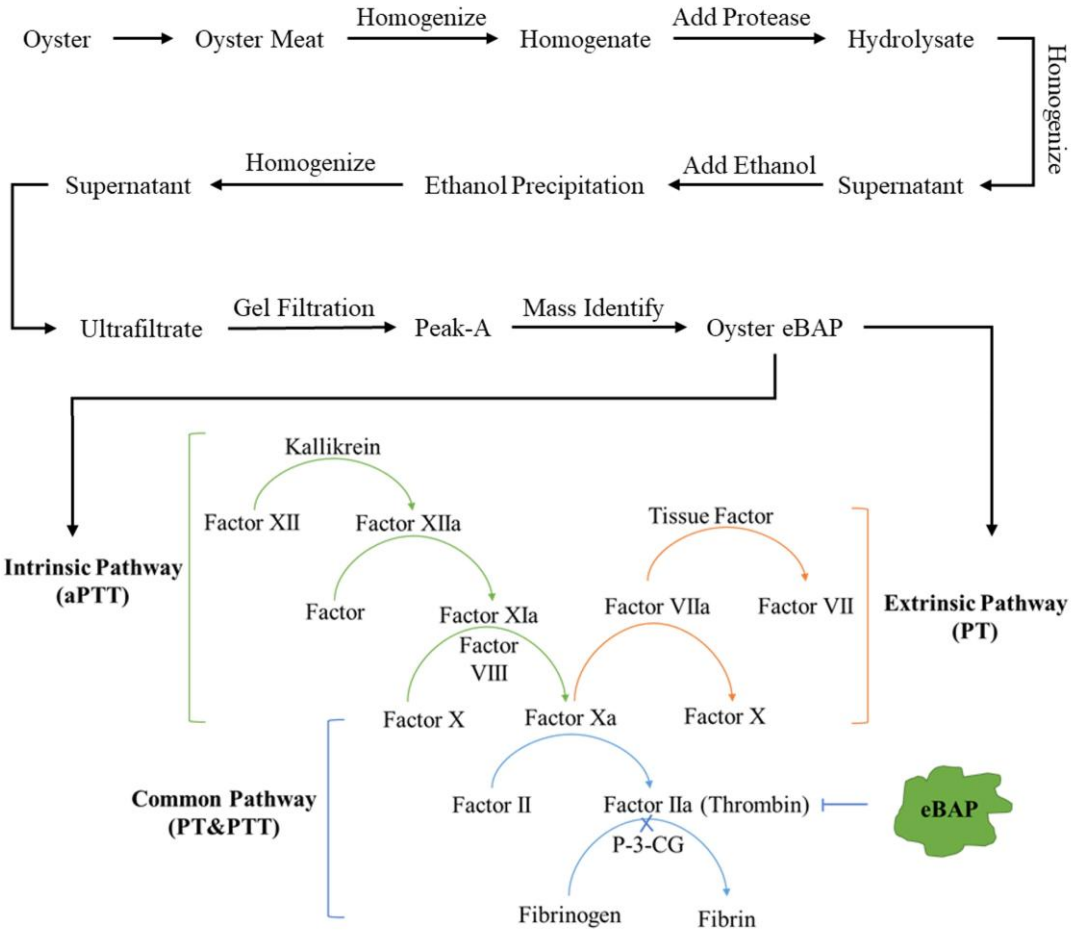

Figure 2. Anticoagulant mechanism of eBAPs.

soybean-derived eBAPs regulate atherosclerotic pathways; and (2) their downstream targets in lipid homeostasis modulation. This mechanistic understanding will be critical for enabling clinical translation and optimising industrial-scale production of soybean eBAP-based functional ingredients.

eBAPs and hypertension

Numerous types of food proteins, including milk, fish, meat, eggs, and various vegetables, have been a source of anti-hypertensive peptides (Fahmi *et al*., 2004; Zhao *et al*., 2009; Hernandez-Ledesma *et al*., 2011). These peptides exert their effects by inhibiting renin or angiotensin-converting enzyme (ACE) activity, as shown in Figure 3. Among the different food sources, dairy eBAPs have been extensively studied as an anti-hypertensive peptide. Additionally, marine eBAPs have garnered significant interest among researchers (Liu *et al*., 2023b; Chen *et al*., 2024; Patil *et al*., 2024; Saraswat and Chugh, 2024). It has been observed that several marine eBAPs inhibited the activities of ACE in spontaneously hypertensive rats (Fahmi *et al*., 2004; Zhao *et al*., 2009). Generally, the administration of marine eBAPs (10 mg/kg) orally leads to an average decreased of 21 - 25 mmHg in systolic blood pressure. The antihypertensive effect of the blood pressure-lowering eBAPs is comparable to that of captopril, a widely available antihypertensive medication (Lee *et al*., 2010). Furthermore, the rats did not exhibit any adverse effects after consuming the eBAPs that lowered blood pressure. However, the therapeutic potential of marine-derived eBAPs as antihypertensive agents remains to be clinically validated, as no randomised controlled trials have been conducted to date. Presently, several natural ACE inhibitor products derived from marine eBAPs have been introduced as dietary supplements to support optional blood pressure levels (Oh *et al*., 2020; Im and Lee 2023; Lee *et al*., 2023). Examples of these products include bonito peptides, Vasotensin®, and PeptAce™ fish peptides, all of which are derived from bonito muscle (Chan *et al*., 2022; Xu *et al*., 2022) (*katsuobushi*). The primary

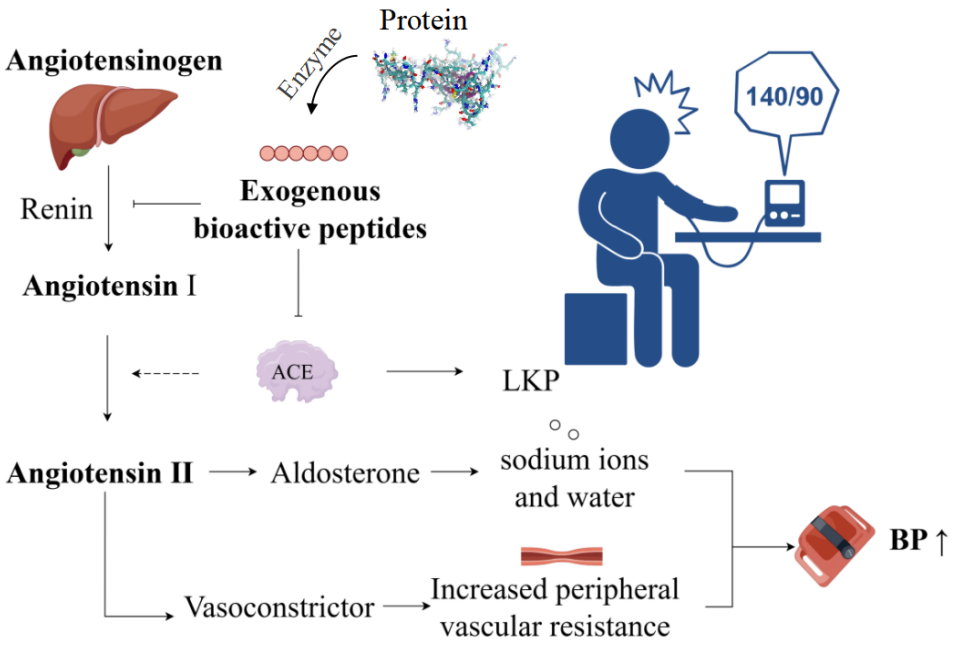

Figure 3. Roles and mechanisms of eBAPs in regulating blood pressure. Drawn by www.figdraw.com.

active oligopeptide found in bonito is LKPNM, which undergoes conversion to LKP by ACE, as shown in Figure 3. This *katsuobushi* oligopeptide has the ability to maintain healthy blood pressure levels. When administered orally, LKPNM exhibited long-lasting and dose-dependent antihypertensive effects in spontaneously hypertensive rats. Clinical studies have been shown that it did not appear to cause any side effects, possibly due to its different mechanisms of ACE inhibition compared to drugs (Fujita *et al*., 2001). Seki (2016) isolated 14 highly inhibitory peptides from the bonito peptide, and demonstrated their potent inhibitory and antihypertensive activities both *in vitro* and *in vivo*. Moreover, a human study was conducted, which revealed no adverse effects based on physician interviews, subjective symptoms, and the absence of drug-specific dry cough. Additionally, haematology and blood biochemistry tests did not uncover any safety concerns. These findings indicated that the peptide could be utilised as a functional food ingredient with a recommended daily intake of 125 mg (Seki, 2016). Furthermore, cricket eBAPs have the ability to inhibit the activities of ACE, α-glucosidase, and α-amylase, thereby reducing inflammation and hypertension (Hall and Liceaga, 2020). Scalable production of this peptide currently faces significant technological constraints. In addition, comparative functional analyses of eBAPs across different cricket species remain to be systematically conducted to elucidate potential bioactivity variations.

Various commercial anti-hypertensive products have been developed (Hossain *et al*., 2020; Kaur *et al*., 2023), including peptide C12, which contains a milk-derived eBAP (FFVAPFPGVFGK). This product has shown the ability to lower blood pressure in individuals with pre-hypertension (borderline hypertension) (Cadée *et al*., 2007), and may have a preventive role in hypertension. Importantly, C12 peptide has been found to be well-tolerated, with no reported adverse effects such as dry cough, skin issues, or gastrointestinal symptoms. These findings highlighted the safety and effectiveness of C12 peptide as a blood pressure-lowering ingredient for human consumption. While antihypertensive peptides are not expected to replace traditional medications in the near future, the ongoing research and development of novel and appealing functional foods remains crucial.

eBAPs and type 2 diabetes

Type 2 diabetes is a complex condition influenced by multiple factors (Mitkin *et al*., 2022; Wu *et al*., 2022; Yi *et al*., 2023; Ibrahim *et al*., 2023). To address this, various anti-diabetic eBAPs derived from functional foods have been utilised in the development of anti-diabetic supplements. In an animal model of metabolic disease, the eBAP CHM-273S demonstrated the ability to improve glucose intolerance and insulin resistance in hepatocytes of rats fed a high-sucrose diet (Mitkin *et al*., 2022; Pavshintsev *et al*., 2022). Furthermore, CHM-273S

was found to induce the phosphorylation of protein kinase B at Ser473 and Thr308. In a murine model of type 2 diabetes, CHM-273S effectively mitigated high-fat diet-induced hyperglycaemia and insulin resistance, while also reducing low-grade inflammation by decreasing serum tumour necrosis factor α levels. Additionally, soybean eBAP was shown to activate the p-Akt/GLUT4 signalling pathway, thereby reducing insulin resistance in 3T3-L1 adipocytes (Wu *et al*., 2022; Yi *et al*., 2023). Yam (AVIAIMF and GPADPF) and taro (NGDF and NGNW) have been identified as sources of anti-diabetic eBAPs. These peptides have demonstrated a higher inhibitory activity against dipeptidyl peptidase IV (DPP-IV) compared to vegliptin, with NGDF exhibiting the highest activity, as shown in Figure 4. AVIAIMF, GPADPF, and NGNW have also shown significantly inhibitory effects on the formation of advanced glycation end products (AGEs) induced by methylglyoxal. Additionally, AVIAIMF and NGNW have exhibited oxygen radical scavenging (ORAC) activity. These peptides have also demonstrated significant nitric oxide clearance activity in mouse macrophages (RAW 264.7) cells, without causing cytotoxicity. Overall, AVIAIMF, GPADPF, and NGNW possess multifunctional potential in combating type 2 diabetes, and have the potential to be utilised as anti-diabetic peptides in functional foods for diabetes prevention (Ibrahim *et al*., 2023).

The administration of clam eBAPs has shown significant improvement in glucose tolerance abnormalities and reduction in the mRNA expression of liver enzymes related to gluconeogenesis and lipogenesis in obesogenic wild-type mice (Kim *et al*., 2022). Peptides VLP, LLP, LL, and LL derived from peas have been found to regulate insulin-induced glucose metabolism in IR-HepG2 cells through the IRS-1/PI3K/AKT and p38MAPK signalling pathways (Zhu *et al*., 2020). Rats with metabolic syndrome experienced a slower rate of weight gain when consuming egg eBAPs, although their food intake remained unchanged (Gewehr *et al*., 2020). eBAPs exhibit their anti-diabetic potential through various mechanisms, include the inhibition of digestive enzymes, control of DPP-IV, reduction of blood sugar levels, and enhancement of insulin uptake (Kehinde and Sharma, 2020), as shown in Figure 4. Currently, there is ongoing screening and identification of various anti-glyco peptides.

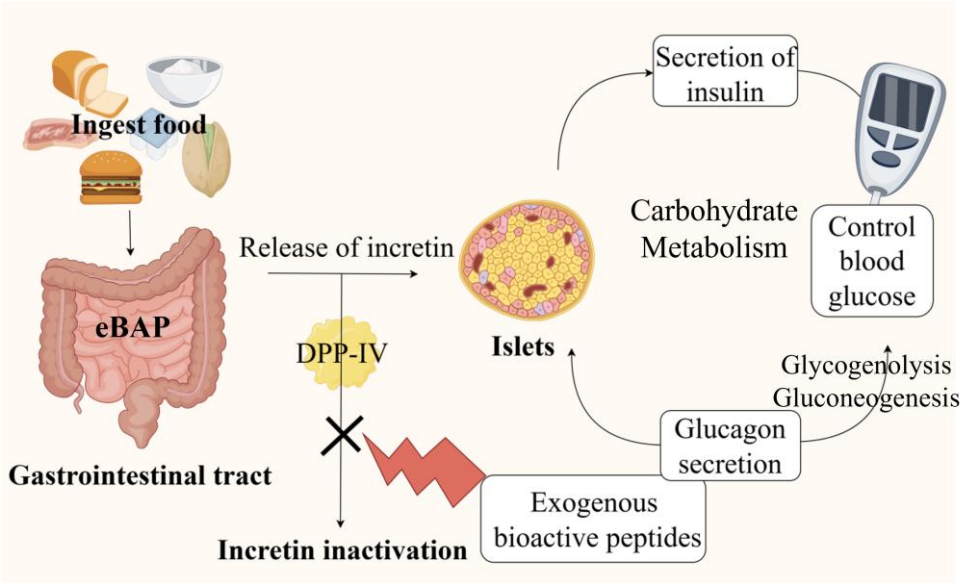

Figure 4. Roles and mechanisms of eBAPs in controlling blood glucose. Drawn by www.figdraw.com.

Conclusion

The present review discussed the biological activity of eBAPs and their physiological regulation on obesity and obesity-related diseases. However, the specific mechanism of reducing fat deposition by eBAPs remains to be studied further. In the future, eBAPs, which can reduce fat deposition and improve metabolic diseases, should be widely screened in daily food. Peptide drugs have garnered significant attention in the medical and pharmaceutical industries due to their rich nutrient profiles, diverse health benefits, and high safety with minimal side effects. eBAPs are a functional component with great potential for the development of functional products and therapeutic drugs. eBAPs are also good candidate

for reducing obesity and obesity-related diseases such as cardiovascular disease, hypertension, and diabetes. At the same time, new eBAPs are constantly being identified from foods or other animal proteins, opening up a vast space for the peptide market. Compared to proteins, eBAPs have greater benefits, more diverse ways to obtain, and relatively safe, but at the same time, the production and commercialisation of eBAPs and their products face great challenges. The bioactive functions of eBAPs and their clinical and safety evaluation as a health food are critical. Most peptide drugs need to be injected into the body, and there are specific requirements for how they are ingested, so eBAPs are unlikely to replace traditional drugs anytime soon.

New eBAPs are still waiting to be discovered and explored, and there are still significant limitations to their development. At present, most of the research on eBAPs is still in the laboratory stage, even though they have broad applications as functional foods and medicines. Chemical modification of the obtained eBAPs structure can be considered to improve their activity and make their performance more stable, which is conducive to market development and utilisation. However, the relationship between structural properties and functional activity has not been fully elucidated. eBAPs have different effects in different molecular weight ranges, and they can be obtained by different hydrolysis methods with specific functions. Although there are still many problems with the application of eBAPs in the treatment of human diseases. Some toxic and sensitising active peptides causing harm to the human body, commercially produced eBAPs lacking quality stability between batches, and human gastrointestinal digestion and rapid metabolism of plasma, liver, and kidney make the efficacy of eBAPs *in vivo* not guaranteed (poor stability), as well as other problems which limit the development of polypeptides. In the future, we can conduct extensive research on eBAPs to improve the system.

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References

Abeer, M. M., Trajkovic, S. and Brayden, D. J. 2021. Measuring the oral bioavailability of protein hydrolysates derived from food sources: A critical review of current bioassays. Biomedicine and Pharmacotherapy 144: 112275.

Acevedo-Juárez, S., Guajardo-Flores, D., Heredia-Olea E. and Antunes-Ricardo, M. 2022. Bioactive peptides from nuts: A review. International Journal of Food Science and Technology 57: 2226-2234.

Alvarez-Vinas, M., Rodriguez-Seoane, P., Florez-Fernandez, N., Dolores Torres, M., Diaz-Reinoso, B., Moure, A. and Dominguez, H. 2021. Subcritical water for the extraction and hydrolysis of protein and other fractions in biorefineries from agro-food wastes and algae: A review. Food and Bioprocess Technology 14: 373-387.

Amigo, L. and Hernandez-Ledesma, B. 2020. Current evidence on the bioavailability of food bioactive peptides. Molecules 25: 4479.

Ashaolu, T. J. 2020. Health applications of soy protein hydrolysates. International Journal of Peptide Research and Therapeutics 26: 2333-2343.

Banfi, C., Mallia, A., Ghilardi, S., Brioschi, M., Gianazza, E., Eligini, S., … and Baetta, R. 2023. Prenylcysteine oxidase 1 is a key regulator of adipogenesis. Antioxidants 12(3): 542.

Cadée, J. A., Chang, C. Y., Chen, C. W., Huang, C. N., Chen, S. L. and Wang, C. K. 2007. Bovine casein hydrolysate (C12 peptide) reduces blood pressure in prehypertensive subjects. American Journal of Hypertension 20: 1-5.

Caponio, G. R., Wang, D. Q., Di Ciaula, A., De Angelis, M. and Portincasa, P. 2020. Regulation of cholesterol metabolism by bioactive components of soy proteins: Novel translational evidence. International Journal of Molecular Sciences 22(1): 227.

Cermeño, M., Connolly, A., O'Keeffe, M. B., Flynn, C., Alashi, A. M., Aluko, R. E. and FitzGerald. R. J. 2019. Identification of bioactive peptides from brewers' spent grain and contribution of Leu/Ile to bioactive potency. Journal of Functional Foods 60: 103455.

Chan, P. T., Matanjun, P., Budiman, C., Shapawi, R. and Lee, J. S. 2022. Novel peptide sequences with ACE-inhibitory and antioxidant activities derived from the heads and bones of hybrid groupers (*Epinephelus lanceolatus* × *Epinephelus fuscoguttatus*). Foods 11(24): 3991.

Chandika, P., Tennakoon, P., Kim, T. H., Kim, S. C., Je, J. Y., Kim, J. I., … and Jung, W. K. 2022. Marine biological macromolecules and chemically modified macromolecules; potential anticoagulants. Marine Drugs 20: 654.

Chang, Y., Dong, M., Wang, Y., Yu, H., Sun, C., Jiang, X., … and Jin, N. 2019. GLP-1 gene-modified human umbilical cord mesenchymal stem cell line improves blood glucose level in type 2 diabetic mice. Stem Cells International 2019: 4961865.

Chen, Z. X., Zhang, L. Z., Liu, Y. N., Wen, Y. X., Shan, S. and Zhao. C. 2024. Seaweed as a sustainable future food source. International Journal of Food Science and Technology 59(3): 1237-1247.

Cheng, S. Z., Tu, M. L., Liu, H. X., An, Y., Du, M. and Zhu, B. W. 2021. A novel heptapeptide derived from *Crassostrea gigas* shows anticoagulant activity by targeting for thrombin active domain. Food Chemistry 334: 127507.

Cheng, S., Tu, M., Chen, H., Xu, Z., Wang, Z., Liu, H., … and Du, M. 2018. Identification and inhibitory activity against α-thrombin of a novel anticoagulant peptide derived from oyster (*Crassostrea gigas*) protein. Food and Function 9: 6391-6400.

Chernukha, I., Kotenkova, E., Derbeneva, S. and Khvostov, D. 2021. Bioactive compounds of porcine hearts and aortas may improve cardiovascular disorders in humans. International Journal of Environmental Research and Public Health 18(14): 7330.

Cruz-Casas, D. E., Aguilar, C. N., Ascacio-Valdés, J. A., Rodríguez-Herrera, R., Chávez-González, M. L. and Flores-Gallegos, A. C. 2021. Enzymatic hydrolysis and microbial fermentation: The most favorable biotechnological methods for the release of bioactive peptides. Food Chemistry 3: 100047.

Cunha, S. A. and Pintado, M. E. 2022. Bioactive peptides derived from marine sources: Biological and functional properties. Trends in Food Science and Technology 119: 348-370.

Dave, L. A., Hayes, M., Montoya, C. A., Rutherfurd, S. M. and Moughan, P. J. 2016. Human gut endogenous proteins as a potential source of angiotensin-I-converting enzyme (ACE-I)-, renin inhibitory and antioxidant peptides. Peptides 76: 30-44.

Dave, L. A., Hayes, M., Mora, L., Rutherfurd, S. M., Montoya, C. A. and Moughan, P. J. 2021. Bioactive peptides originating from gastrointestinal endogenous proteins in the growing pig: *In vivo* identification. Current Pharmaceutical Design 27(11): 1382-1395.

Delgadillo-Puga, C., Noriega, L. G., Morales-Romero, A. M., Nieto-Camacho, A., Granados-Portillo, O., Rodríguez-López, L. A., … and Torre-Villalvazo, I. 2020. Goat's milk intake prevents obesity, hepatic steatosis and insulin resistance in mice fed a high-fat diet by reducing inflammatory markers and increasing energy expenditure and mitochondrial content in skeletal muscle. International Journal of Molecular Sciences 21(15): 5530.

Dominguez-Perez, L. A., Beltran-Barrientos, L. M., Gonzalez-Cordova, A. F., Hernandez-Mendoza, A. and Vallejo-Cordoba, B. 2020. Artisanal cocoa bean fermentation: From cocoa bean proteins to bioactive peptides with potential health benefits. Journal of Functional Foods 73: 104134.

Ejike, C. E. C. C., Ezeorba, T. P. C., Ajah, O. and Udenigwe, C. C. 2023. Big things, small packages: An update on microalgae as sustainable sources of nutraceutical peptides for promoting cardiovascular health. Global Challenges 7(5): 2200162.

El Meouchy, P., Wahoud, M., Allam, S., Chedid, R., Karam, W. and Karam, S. 2022. Hypertension related to obesity: Pathogenesis, characteristics and factors for control. International Journal of Molecular Sciences 23(20): 12305.

Fahmi, A., Morimura, S., Guo, H. C., Shigematsu, T., Kida, K. and Uemura, Y. 2004. Production of angiotensin I converting enzyme inhibitory peptides from sea bream scales. Process Biochemistry 39: 1195-1200.

Froetschel, M. A., Azain, M. J., Edwards, G. L., Barb, C. R. and Amos, H. E. 2001. Opioid and cholecystokinin antagonists alleviate gastric

inhibition of food intake by premeal loads of casein in meal-fed rats. The Journal of Nutrition 131(12): 3270-3276.

Fujita, H., Yamagami, T. and Ohshima, K. 2001. Effects of an ace-inhibitory agent, katsuobushi oligopeptide, in the spontaneously hypertensive rat and in borderline and mildly hypertensive subjects. Nutrition Research 21: 1149-1158.

Gewehr, M. C. F., Silverio, R., Rosa-Neto, J. C., Lira, F. S., Reckziegel, P. and Ferro, E. S. 2020. Peptides from natural or rationally designed sources can be used in overweight, obesity, and type 2 diabetes therapies. Molecules 25(5): 1093.

Goldsborough, E., Osuji, N. and Blaha, M. J. 2022. Assessment of cardiovascular disease risk. Endocrinology and Metabolism Clinics of North America 51: 483-509.

Guo, L., Park, S. Y., Kang, H. M., Kang, N. J., Hwang, D. Y. and Choi, Y. W. 2022. Edible vitalmelon fruit extract inhibits adipogenesis and ameliorates high-fat diet-induced obesity. BioMed Research International 2022: 2369650.

Haidar, A. and Horwich, T. 2023. Obesity, cardiorespiratory fitness, and cardiovascular disease. Current Cardiology Reports 25(11): 1565-1571.

Hall, F., and Liceaga, A. 2020. Effect of microwave-assisted enzymatic hydrolysis of cricket (*Gryllodes sigillatus*) protein on ACE and DPP-IV inhibition and tropomyosin-IgG binding. Journal of Functional Foods 64: 103634.

Hernandez-Ledesma, B., Ramos, M. and Gomez-Ruiz, J. A. 2011. Bioactive components of ovine and caprine cheese whey. Small Ruminant Research 101: 196-204.

Hossain, A., Dave, D. and Shahidi, F. 2020. Northern sea cucumber (*Cucumaria frondosa*): A potential candidate for functional food, nutraceutical, and pharmaceutical sector. Marine Drugs 18: 274.

Hu, S., Liu, C. and Liu, X. 2023. The beneficial effects of soybean proteins and peptides on chronic diseases. Nutrients 15(8): 1811.

Ibrahim, M. A., Serem, J. C., Abdullahi, A. D., Aminu, S., Aliyu, A. B., Musa, A. M., … and Gaspar, A. R. M. 2023. Bioactive peptides from African yam (AVIAIMF and GPADPF) and taro (NGDF and NGNW) reveal multifunctional antidiabetic effects using biochemical and cellular models. International Journal of Peptide Research and Therapeutics 29: 46.

Im, S. T. and Lee, S. H. 2023. Structure characterization and antihypertensive effect of an antioxidant peptide purified from alcalase hydrolysate of velvet antler. Food Science of Animal Resources 43: 184-194.

Jakubowicz, D. and Froy, O. 2013. Biochemical and metabolic mechanisms by which dietary whey protein may combat obesity and type 2 diabetes. Journal of Nutritional Biochemistry 24: 1-5.

Kaneko, K., Takekuma, Y., Goto, T. and Ohinata, K. 2022. An orally active plant Rubisco-derived peptide increases neuronal leptin responsiveness. Scientific Reports 12(1): 8599.

Karakurt, H. U. and Pir, P. 2023. Machine learning based bioinformatics analysis of intron usage alterations and metabolic regulation in adipose browning. Turkish Journal of Electrical Engineering and Computer Sciences 31: 1314-1328.

Karelin, A. A., Blishchenko, E. and Ivanov, V. T. 1998. A novel system of peptidergic regulation. FEBS Letters 428(1-2): 7-12.

Kaur, M., Bhatia, S., Gupta, U., Decker, E., Tak, Y., Bali, M., … and Bala, S. 2023. Microalgal bioactive metabolites as promising implements in nutraceuticals and pharmaceuticals: Inspiring therapy for health benefits. Phytochemistry Reviews 22: 903-933.

Kehinde, B. A. and Sharma, P. 2020. Recently isolated antidiabetic hydrolysates and peptides from multiple food sources: A review. Critical Reviews in Food Science and Nutrition 60: 322-340.

Kim, M. J., Chilakala, R., Jo, H. G., Lee, S. J., Lee, D. S. and Cheong, S. H. 2022. Anti-obesity and anti-hyperglycemic effects of *Meretrix lusoria* protamex hydrolysate in *ob/ob* mice. International Journal of Molecular Sciences 23(7): 4015.

Koirala, P., Dahal, M., Rai, S., Dhakal, M., Nirmal, N. P., Maqsood, S., … and Buranasompob, A. 2023. Dairy milk protein-derived bioactive peptides: Avengers against metabolic syndrome. Current Nutrition Reports 12(2): 308-326.

Koliaki, C., Liatis, S. and Kokkinos, A. 2019. Obesity and cardiovascular disease: Revisiting an old relationship. Metabolism-Clinical and Experimental 92: 98-107.

Lee, E. Y. and Yoon, K. H. 2018. Epidemic obesity in children and adolescents: Risk factors and prevention. Frontiers of Medicine 12: 658-666.

Lee, J. H., Kim, T. K., Yong, H. I., Cha, J. Y., Song, K. M., Lee, H. G., … and Choi, Y. S. 2023. Peptides inhibiting angiotensin-I-converting enzyme: Isolation from flavourzyme hydrolysate of *Protaetia brevitarsis* larva protein and identification. Food Chemistry 399: 133897.

Lee, S. H., Qian, Z. J. and Kim, S. K. 2010. A novel angiotensin I converting enzyme inhibitory peptide from tuna frame protein hydrolysate and its antihypertensive effect in spontaneously hypertensive rats. Food Chemistry 118: 96-102.

Lin, W. T., Nithiyanantham, S., Hsieh, D. J., Chen, R. J., Day, C. H., Liao, J. Y., … and Huang, C. Y. 2020. Bioactive peptides attenuate cardiac apoptosis in spontaneously hypertensive rat hearts through activation of autophagy and mitochondrial biogenesis pathway. Environmental Toxicology 35(7): 804-810.

Liu, L., Chen, Y., Chen, B., Xu, M., Liu, S., Su, Y., … and Liu, Z. 2023b. Advances in research on marine-derived lipid-lowering active substances and their molecular mechanisms. Nutrients 15: 5118.

Liu, L., Yu, S., Bu, T., He, G., Li, S. and Wu, J. 2023a. Casein hydrolysate alleviates adipose chronic inflammation in high fat-diet induced obese C57BL/6J mice through MAPK pathway. Nutrients 15: 1813.

Lordan, S., Ross, R. P. and Stanton, C. 2011. Marine bioactives as functional food ingredients: Potential to reduce the incidence of chronic diseases. Marine Drugs 9: 1056-1100.

Ma, Y., Yu, H., Xing, R., Liu, S. and Li, P. 2023. Lipid-lowering activity and mechanism of peptides from jellyfish *Nemopilema nomurai*. Journal of Functional Foods 101: 105421.

Mallah, M. A., Soomro, T., Noreen, S., Ali, M., Kafle, A., Khatoon, N. and Naveed, M. 2023. Association of obesity and cardiovascular disease and progress in pharmacotherapy: what is next for obesity? International Journal of Rehabilitation Research 46: 14-25.

Manzoor, M., Singh, J. and Gani, A. 2022. Exploration of bioactive peptides from various origin as promising nutraceutical treasures: *In vitro*, *in silico* and *in vivo* studies. Food Chemistry 373: 131395.

Markoulli, M., Ahmad, S., Arcot, J., Arita, R., Benitez-Del-Castillo, J., Caffery, B., … and Wolffsohn, J. S. 2023. TFOS lifestyle: Impact of nutrition on the ocular surface. Ocular Surface 29: 226-271.

Mathew, B., Francis, L., Kayalar, A. and Cone, J. 2008. Obesity: Effects on cardiovascular disease and its diagnosis. Journal of the American Board of Family Medicine 21: 562-568.

Mathis, B. J., Tanaka, K. and Hiramatsu, Y. 2023. Metabolically healthy obesity: Are interventions useful. Current Obesity Reports 12: 36-60.

Matsui, T. 2018. Are peptides absorbable compounds? Journal of Agricultural and Food Chemistry 66: 393-394.

Mellinkoff, S. M., Frankland, M., Boyle, D. and Greipel, M. 1956. Relationship between serum amino acid concentration and fluctuations in appetite. Journal of Applied Physiology 8: 535-538.

Miner-Williams, W. M., Stevens, B. R. and Moughan, P. J. 2014. Are intact peptides absorbed from the healthy gut in the adult human? Nutrition Research Reviews 27: 308-329.

Mitkin, N. A., Pavshintcev, V. V., Sukhanova, I. A., Doronin, I. I., Babkin, G. A., Sadagurski, M. and Malyshev, A. V. 2022. The novel peptide Chm-273s has therapeutic potential for metabolic disorders: Evidence from *in vitro* studies and high-sucrose diet and high-fat diet rodent models. Pharmaceutics 14(10): 2088.

Monsalve, F. A., Delgado-López, F., Fernández-Tapia, B. and González, D. R. 2023. Adipose tissue, non-communicable diseases, and physical exercise: An imperfect triangle. International Journal of Molecular Sciences 24: 17168.

Moreira, L. P. D., Corich, V., Jørgensen, E. G., Devold, T. G., Nadai, C., Giacomini, A. and Porcellato, D. 2024. Potential bioactive peptides obtained after *in vitro* gastrointestinal

digestion of wine lees from sequential fermentations. Food Research International 176: 113833.

Nagaoka, S., Takeuchi, A. and Banno, A. 2021. Plant-derived peptides improving lipid and glucose metabolism. Peptides 142: 170577.

Nikiforaki, K., and Marias, K. 2023. MRI methods to visualize and quantify adipose tissue in health and disease. Biomedicines 11: 3179.

Nongonierma, A. B., Schellekens, H., Dinan, T. G., Cryan, J. F. and FitzGerald, R. J. 2013. Milk protein hydrolysates activate 5-HT(2C) serotonin receptors: Influence of the starting substrate and isolation of bioactive fractions. Food and Function 4(5): 728-737.

Oh, J. Y., Je, J. G., Lee, H. G., Kim, E. A., Kang, S. I., Lee, J. S. and Jeon, Y. J. 2020. Anti-hypertensive activity of novel peptides identified from olive flounder (*Paralichthys olivaceus*) surimi. Foods 9(5): 647.

Oliveira, A. S., Pereira, A. M., Ferreira, C. M. H., Pereira, J. O., Amorim, M., Faustino, M., … and Carvalho, A. P. 2024. Purification of bioactive peptides from spent yeast autolysates. Food and Bioproducts Processing 143: 45-53.

Öztürk, H. I., Orac, A. and Akin, N. 2022. Characterization of bioactive peptides derived from goatskin Tulum cheese of the Ereğli region at different stages of ripening. Food Research International 162: 112124.

Patil, P. J., Usman, M., Zhang, C., Mehmood, A., Zhou, M., Teng, C. and Li, X. 2022. An updated review on food-derived bioactive peptides: Focus on the regulatory requirements, safety, and bioavailability. Comprehensive Reviews in Food Science and Food Safety 21: 1732-1776.

Patil, U., Nilsuwan, K. and Benjakul, S. 2024. Functional ingredients from seafood processing wastes: Protein hydrolysate and biocalcium. Turkish Journal of Fisheries and Aquatic Sciences 24: TRJFAS25347.

Pavshintsev, V., Mitkin, N., Doronin, I., Emelianova, E., Lovat, M., Babkin, G. and Malyshev, A. 2022. CHM-273S peptide decreases blood glucose level, improves insulin sensitivity, and induces insulin signaling pathways in the liver of rats with diet-induced metabolic disorder. Diabetes 71: 111-LB.

Peighambardoust, S. H., Karami, Z., Pateiro, M. and Lorenzo, J. M. 2021. A review on health-promoting, biological, and functional aspects of bioactive peptides in food applications. Biomolecules 11: 631.

Räder, A. F. B., Weinmüller, M., Reichart, F., Schumacher-Klinger, A., Merzbach, S., Gilon, C., … and Kessler, H. 2018. Orally active peptides: Is there a magic bullet? Angewandte Chemie 57(44): 14414-14438.

Rafiq, S., Huma, N., Pasha, I., Shahid, M. and Xiao, H. 2017. Angiotensin-converting enzyme-inhibitory and antithrombotic activities of soluble peptide extracts from buffalo and cow milk Cheddar cheeses. International Journal of Dairy Technology 70: 380-388.

Ren, Y., Wu, H., Lai, F., Yang, M., Li, X. and Tang, Y. 2014. Isolation and identification of a novel anticoagulant peptide from enzymatic hydrolysates of scorpion (*Buthus martensii* Karsch) protein. Food Research International 64: 931-938.

Rengasamy, K. R. R., Khan, H., Ahmad, I., Lobine, D., Mahomoodally, F., Suroowan, S., … and Pandian, S. K. 2019. Bioactive peptides and proteins as alternative antiplatelet drugs. Medicinal Research Reviews 39: 2153-2171.

Saraswat, S., and Chugh, A. 2024. Engraulisin: A novel marine derived cell penetrating peptide with activity against drug resistant bacteria. Biochimica Et Biophysica Acta - Biomembranes 1866: 184255.

Seki, E. 2016. Anti-hypertensive peptide derived from *katsuobushi*. Journal of Hypertension 34: E430-E431.

Siddik, M. A. B., Howieson, J., Fotedar, R. and Partridge, G. J. 2021. Enzymatic fish protein hydrolysates in finfish aquaculture: A review. Reviews in Aquaculture 13: 406-430.

Song, Y., Cai, Q., Wang, S., Li, L., Wang, Y., Zou, S., … and Wei, Y. 2022. The ameliorative effect and mechanisms of *Ruditapes philippinarum* bioactive peptides on obesity and hyperlipidemia induced by a high-fat diet in mice. Nutrients 14(23): 5066.

Sotoudeh, B. and Azizi, M. H. 2023. Production of bioactive peptides with antioxidant and antihypertensive activities from wheat gluten using *Withania coagulans*. Journal of Food Measurement and Characterization 18:

2101-2109.

Sridhar, K., Inbaraj, B. S. and Chen, B. H. 2021. Recent developments on production, purification and biological activity of marine peptides. Food Research International 147: 110468.

Suryaningtyas, I. T. and Je, J. Y. 2023. Bioactive peptides from food proteins as potential anti-obesity agents: Mechanisms of action and future perspectives. Trends in Food Science and Technology 138: 141-152.

Tadesse, S. A. and Emire, S. A. 2020. Production and processing of antioxidant bioactive peptides: A driving force for the functional food market. Heliyon 6: e04765.

Tanikawa, K., Kaneko, K., Abe, S., Nakato, J., Tokuyama, Y., Odaka, S., … and Ohinata, K. 2021. Wheat-ghretropins: Novel ghrelin-releasing peptides derived from wheat protein. FEBS Open Bio 11: 1144-1152.

Tasdemir, S. S. and Sanlier, N. 2020. An insight into the anticancer effects of fermented foods: A review. Journal of Functional Foods 75: 104281.

Tian, X., Chen, S., Wang, P., Xu, Q., Zhang, Y., Luo, Y., … and Wang, A. 2022. Insulin resistance mediates obesity-related risk of cardiovascular disease: a prospective cohort study. Cardiovascular Diabetology 21: 289.

Tsou, M. J., Kao, F. J., Lu, H. C., Kao, H. C. and Chiang, W. D. 2013. Purification and identification of lipolysis-stimulating peptides derived from enzymatic hydrolysis of soy protein. Food Chemistry 138: 1454-1460.

Ulug, S. K., Jahandideh, F. and Wu, J. 2021. Novel technologies for the production of bioactive peptides. Trends in Food Science and Technology 108: 27-39.

Von Heesen, M. 2022. Indications in obesity therapy-surgeons first? Zentralblatt für Chirurgie 147: 525-538.

Wang, S., Zhao, M., Fan, H. and Wu, J. 2023a. Peptidomics study of plant-based meat analogs as a source of bioactive peptides. Foods 12: 1061.

Wang, W., Yang, W., Dai, Y., Liu, J. and Chen, Z. Y. 2023b. Production of food-derived bioactive peptides with potential application in the management of diabetes and obesity: A review. Journal of Agricultural and Food Chemistry 71: 5917-5943.

Wang, X., Yu, H., Xing, R. and Li, P. 2017. Characterization, preparation, and purification of marine bioactive peptides. Biomed Research International 2017: 9746720.

Wei, K., Wei, Y., Xu, W., Lu, F. and Ma, H. 2022. Corn peptides improved obesity-induced non-alcoholic fatty liver disease through relieving lipid metabolism, insulin resistance and oxidative stress. Food and Function 13: 5782-5793.

Wu, Y., Zhao, R., Li, M., Li, H., Chen, Z. and Zhao, Y. 2022. Novel soybean peptide iglycin ameliorates insulin resistance of high-fat diet fed C57BL/6J mice and differentiated 3T3L1 adipocytes with improvement of insulin signaling and mitochondrial function. Food Science and Human Wellness 11: 1565-1572.

Xu, Q. B., Hong, H., Wu, J. P. and Yan, X. H. 2019. Bioavailability of bioactive peptides derived from food proteins across the intestinal epithelial membrane: A review. Trends in Food Science and Technology 86: 399-411.

Xu, X. Q., Zhou, Q., Sun, J. H., Sun, L. X., Feng, X. Z., Xu, Y. F., … and Liao, D. K. 2022. Study on the inhibition mechanism of angiotensin conversion enzyme inhibitor peptide Leu-Lys-Pro (LKP). Spectroscopy and Spectral Analysis 42: 2107-2112.

Yang, L., Zhang, L., Yan, L., Zheng, H., Lu, P., Chen, J., … and Yang, T. 2017. Stability assessment of a new antithrombotic small peptide, Arg-Gly-Asp-Trp-Arg (RGDWR), and its derivative. Biotechnology Letters 39: 1183-1190.

Yi, G., Sang, X., Zhu, Y., Zhou, D., Yang, S., Huo, Y., … and Bu, X. 2023. The SWGEDWGEIW from soybean peptides reduces insulin resistance in 3T3-L1 adipocytes by activating p-Akt/GLUT4 signaling pathway. Molecules 28: 3001.

Yoshikawa, M. 2015. Bioactive peptides derived from natural proteins with respect to diversity of their receptors and physiological effects. Peptides 72: 208-225.

Yuan, X., Li, P. C., Xiao, Z. W. and Lou, W. Y. 2024. Preparation and identification of hypoglycemic bioactive peptide from *Amygdalus communis* L. by multienzyme hydrolysis. Process Biochemistry 136: 292-300.

Zambrowicz, A., Timmer, M., Polanowski, A., Lubec, G. and Trziszka, T. 2013.

Manufacturing of peptides exhibiting biological activity. Amino Acids 44: 315-320.

Zhang, S., Kong, L., Jia, Z., Shao, S., Pan, L., Wang, W. and Sun, Y. 2022. Anti-obesity effects of corn peptide on 3T3-L1 preadipocytes and C57BL/6J obese mice. Archives of Animal Nutrition 76: 205-220.

Zhao, Y., Li, B., Dong, S., Liu, Z., Zhao, X., Wang, J. and Zeng, M. 2009. A novel ACE inhibitory peptide isolated from *Acaudina molpadioidea* hydrolysate. Peptides 30: 1028-1033.

Zhou, M., Zhao, G., Zeng, Y., Zhu, J., Cheng, F. and Liang, W. 2022. Aging and cardiovascular disease: Current status and challenges. Reviews in Cardiovascular Medicine 23(4): 135.

Zhu, Y., Zhang, H., Wei, Y., Cai, M., Gu, R., Wang, Y., … and Chen, L. 2020. Pea-derived peptides, VLP, LLP, VA, and LL, improve insulin resistance in HepG2 cells *via* activating IRS-1/PI3K/AKT and blocking ROS-mediated p38MAPK signaling. Journal of Food Biochemistry 44: e13454.