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Bioactive peptides from food proteins as potential anti-obesity agents: Mechanisms of action and future perspectives

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ABSTRACT

Background: Obesity is a global health concern with limited treatment options due to side effects and limited efficacy. Bioactive peptides (BAPs) derived from food proteins have shown promise as safe and effective anti-obesity agents by regulating adipocyte differentiation through various signaling pathways. BAPs derived from milk, eggs, fish, and marine sources have been extensively studied for their anti-obesity effects *in vitro* and *in vivo*. These peptides can alter gut hormones and appetite to regulate energy balance while decreasing adipogenesis and increasing adipocyte apoptosis.

Scope and approach: This paper provides a comprehensive overview of the studies investigating the potency of BAPs in managing obesity. It focuses on their ability to modulate adipogenesis and regulate appetite and lipid metabolism.

Key findings and Conclusions: BAPs derived from various food sources such as milk, eggs, fish, and marine byproducts have the potential to act as anti-obesity agents. These peptides have been shown to be able to regulate adipogenesis, lipid metabolism, and appetite control through different mechanisms, making them promising candidates for developing functional foods or nutraceuticals for obesity prevention and management. This paper also highlights the advantages of using BAPs over conventional anti-obesity drugs, such as their safety, natural origin, and lower risk of adverse effects. Further research and development in this field can lead to the identification and utilization of specific BAPs with optimized efficacy and minimal side effects, ultimately contributing to the development of novel anti-obesity therapies.

1. Introduction

Adipogenesis is the complex process of preadipocytes maturing into adipocytes, which plays a critical role in regulating energy and metabolic health (Zhao et al., 2022). Adipose tissue is a dynamic and metabolically active endocrine organ that is responsible for the storage and release of fatty acids and the production of adipokines known to play a key role in regulating energy balance and glucose metabolism. Dysregulation of adipogenesis can lead to the development of obesity and related metabolic disorders such as type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (Klein et al., 2022; Shi et al., 2022).

In recent years, there has been a growing interest in using bioactive peptides (BAPs) derived from food proteins as a natural and safe strategy for obesity management. BAPs are short chains of amino acids released during the digestion of food proteins. They have a wide range of physiological effects, including antioxidant, antihypertensive, and antimicrobial properties (Oh et al., 2023; Skjånes et al., 2021; Suryaningtyas et al., 2021). Studies have shown that BAPs can prevent fat accumulation, regulate appetite and energy metabolism, and possess anti-inflammatory and antioxidant properties, making them promising anti-obesity agents (Ahn & Je, 2021; Chaves Filho et al., 2020; Kim et al., 2022; Mudgil et al., 2018; Oh et al., 2023). By comprehensively investigating the mechanisms, evaluating the efficacy, and carefully assessing the potential side effects associated with the utilization of BAPs as anti-obesity agents, we can establish a strong foundation for the development of highly effective and well-tolerated anti-obesity therapies agents.

This paper aims to provide a comprehensive review of current literature on potential anti-obesity effects of BAPs from food proteins.

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Mechanisms of action of these peptides, their sources, and their bioavailability are discussed. In addition, the potential of using BAPs as a novel therapeutic strategy for the management of obesity is evaluated, with a focus on future perspectives and areas for further research.

1.1. Obesity

The prevalence of obesity has been increasing worldwide over the past few decades, making it a major public health concern. According to the World Health Organization (WHO), the global prevalence of obesity nearly tripled between 1975 and 2016, with an estimated 1.9 billion adults overweight and over 650 million of these individuals classified as obese in 2016 (Organization, 2022). Obesity rates continue to increase worldwide, with nearly 40% of adults considered overweight and over 13% considered obese (Organization, 2021). The COVID-19 pandemic has further highlighted the importance of addressing obesity as individuals with obesity have been found to be at higher risk for severe illness and death from COVID-19 (Yu et al., 2022). Childhood obesity is also a growing problem, with an estimated 38 million children under the age of 5 being overweight or obese in 2019 (Apperley et al., 2022). The highest prevalence of obesity has been observed in developed countries such as the United States, Canada, Australia, and Western Europe. Its prevalence is also increasing rapidly in low- and middle-income countries (Apperley et al., 2022).

Efforts to address the obesity epidemic focus on promoting healthy diets, physical activity and treatment through interventions such as behavioral therapy, bariatric surgery, and pharmacotherapy (Klein et al., 2022). Weight loss interventions in the treatments and management of obesity aim to create a negative energy balance. This can be achieved through strategies such as reducing calorie consumption by 500–750 kcal/day or limiting total caloric intake to 1200–1500 kcal/day for women and 1500–1800 kcal/day for men (Johnson et al., 2022). Lifestyle interventions are challenging due to social and environmental factors and individual preferences. People's physiological and genetic factor influence their response to obesity treatments. What works for one person may not work for another, making it difficult to find a universally effective approach. Bariatric surgery carries risks and requires lifelong modifications. Pharmacotherapy medications currently approved by regulatory agencies for obesity treatment include appetite suppressants, such as phentermine, and lipase inhibitors such as orlistat, phentermine/topiramate, liraglutide, and naltrexone/bupropion (Shi et al., 2022). Although these medications can lead to modest weight loss and improvements in metabolic parameters, they might be associated with side effects such as gastrointestinal symptoms, psychiatric disorders, and cardiovascular events (Tak & Lee, 2021).

Given these challenges, there is a need for novel and effective obesity treatments that are safe, sustainable, and accessible. BAPs from food proteins have attracted attention as a promising area of research as they are naturally occurring compounds with potential anti-obesity effects that exhibit diverse mechanisms of action. BAPs have the ability to specifically target and interact with molecular pathways and receptors involved in appetite regulation, lipid metabolism, and adipogenesis. By selectively modulating these pathways, BAPs can effectively regulate energy balance and contribute to weight management. Derived from natural sources, such as food proteins, BAPs are generally considered safe and well-tolerated by the human body. However, further research is needed to determine the efficacy and safety of BAPs for obesity management.

1.2. Adipogenesis transcription factors and signaling pathways

Understanding the mechanisms underlying adipogenesis and factors that influence it is essential for the development of new therapeutic approaches for treating obesity and related metabolic disorders. Adipogenesis is regulated by a complex network of transcription factors, signaling pathways, and epigenetic mechanisms known to be influenced by a variety of intrinsic and extrinsic factors including hormones, cytokines, growth factors, and nutrients (Lee et al., 2019). Since the discovery of leptin, the interest to study the adipose tissue metabolism has increased significantly (Kołodziejski et al., 2021). Several newly discovered peptide hormones such as adropin, apelin, elabela, irisin, kisspeptin, MOTS-c, phoenixin, spexin, and neuropeptides B and W have been recently reported to modulate adipose tissue metabolism (Kołodziejski et al., 2021). This indicate that the elucidation of the intricate interactions between biological compounds, and their respective receptors still remains largely elusive, constituting a captivating field of ongoing research and exploration.

Adipogenesis comprises two distinct phases: commitment and terminal differentiation. During the commitment phase, mesenchymal stem cells (MSCs) undergo a transformation into preadipocytes, which exhibit similar morphology to their precursor cells but lose their capacity to differentiate into other cell types (Khan et al., 2022). This commitment occurs within the vesicular structure of adipose tissue, where MSCs express specific molecular markers, including platelet-derived growth factor receptor (PDGFR) α or/and PDGFRβ. Subsequently, the second step of adipogenesis involves the differentiation of preadipocytes and their maturation into fully functional adipocytes (Zhao et al., 2022).

Transcription factors play a crucial role in regulating gene expression by binding to specific DNA sequences. Among the transcription factors that are currently known, peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα) are two of the most important transcription factors involved in adipogenesis. PPARγ and C/EBPα can promote differentiation of preadipocytes into mature adipocytes by activating the expression of genes involved in lipid metabolism and adipocyte differentiation (Kawai, 2013; Lee et al., 2022). PPARγ activation is required for the differentiation of preadipocytes into mature adipocytes. PPARγ can activate the expression of adipogenic genes and promote lipid accumulation in adipocytes (Farmer, 2005; Kawai, 2013). C/EBPα acts synergisticaly with PPARγ to activate the expression of adipogenic genes and promote lipid accumulation in adipocytes (Farmer, 2005). Sterol regulatory element-binding protein 1c (SREBP-1c) is another important transcription factor that regulates lipid metabolism. It is involved in promoting adipocyte differentiation and lipid accumulation (Shimano, 2009).

Transcription factors can be activated or regulated by various signaling pathways within the cell. Signaling pathways transmit signals from cell surface receptors to the nucleus, where they modulate the activity of transcription factors (Lee et al., 2019). Several signaling pathways have been implicated in adipocyte differentiation, including the Wingless-related integration site (Wnt), transforming growth factor beta (TGF-β), and bone morphogenetic protein (BMP) pathways. These pathways can interact with each other and various transcription factors to regulate different stages of adipogenesis, such as cell proliferation, differentiation, and maturation (De Winter & Nusse, 2021; Zou et al., 2021). The Wnt signaling pathway is involved in regulating adipogenesis by inhibiting the differentiation of preadipocytes. The pathway is activated by Wnt ligands, which can bind to Frizzled receptors and inhibit the expression of adipogenic genes (De Winter & Nusse, 2021). Another pathway is insulin signaling pathway, which can activate the Akt signaling pathway and lead to the activation of PPARγ and C/EBPα (Farmer, 2005). The Hedgehog signaling pathway is also involved in regulating adipocyte differentiation and lipid metabolism (Fontaine et al., 2008). The pathway is activated by Hedgehog ligands, which can bind to Patched receptors and activate the Smoothened receptor. Activation of the Hedgehog signaling pathway can promote adipocyte differentiation and lipid accumulation. AMP-activated protein kinase (AMPK) signaling pathway is an important regulator of energy metabolism. It is involved in regulating adipocyte differentiation and lipid metabolism. Activation of AMPK can inhibit adipocyte differentiation and promote lipolysis (Wang et al., 2020). These transcription factors and signaling pathways work in a coordinated manner to regulate

adipogenesis. Their dysregulation can lead to the development of obesity and metabolic disorders. Dysregulation of PPARγ and C/EBPα transcription factors, which are critical regulators of adipogenesis, can lead to a decrease in adipocyte differentiation and an increase in accumulation of preadipocytes (Farmer, 2005). Conversely, overexpression of these transcription factors can lead to increases of adipocyte differentiation and accumulation of adipose tissue. Various internal and external factors can also influence adipocyte differentiation and function. For example, obesity and insulin resistance are associated with dysregulation of adipogenesis, increased expression of inflammatory cytokines, and decreased expression of adipogenic transcription factors (Ciezniak et al., 2021; Grancieri et al., 2021). Insulin resistance, a common feature of obesity and type 2 diabetes, can impair adipogenesis by reducing the expression of adipogenic genes and increasing the accumulation of preadipocytes (Klein et al., 2022). Epigenetic modifications such as DNA methylation and histone modifications can also dysregulate adipogenesis (Lee et al., 2019). For example, alterations in DNA methylation patterns in key adipogenic genes have been shown to impair adipocyte differentiation and promote accumulation of preadipocytes (Ciezniak et al., 2021). Understanding mechanisms underlying adipogenesis and signaling pathways involved may lead to the development of new therapeutic approaches for treating obesity and related metabolic disorders.

2. BAPs from food

Food protein has long been recognized as a source of both energy and the necessary amino acids required to maintain physiologic function. Amino acid sequences that form protein fragments are joined by peptide bonds known as BAPs (Khan et al., 2022). Sizes of BAPs may varying from 2 to 30 amino acid residues. BAPs can exert different biological activities including antioxidant, anti-inflammatory, antihypertensive, anti-obesity, antibacterial, and immune-modulatory effects once they are released (Ahn & Je, 2021; Palman et al., 2020; Skjånes et al., 2021; Suryaningtyas et al., 2021). Several studies have demonstrated anti-obesity effects of BAPs derived from milk proteins, including regulation of adipogenesis and reduction of adipose tissue accumulation. Up to now, milk and its derivatives are the greatest sources of food BAPs (Hao et al., 2021; Soleymanzadeh et al., 2019), followed by egg (Jahandideh et al., 2019), farm animal meats (Palman et al., 2020; Raju et al., 2021), and marine organism (Henda et al., 2015). BAPs can also be obtained from vegetal food such as soy (Londhe et al., 2011; Marthandam Asokan et al., 2018), wheat (Wang et al., 2020), mushroom (Paisansak et al., 2021), plant (Shang et al., 2021), marine algae (Cian et al., 2022), and microalgae (Skjånes et al., 2021). Several byproducts from food industries can also be used as raw materials for BAPs, such as skin collagen, bones, blood, internal organs, and food processing wastewater (Astre et al., 2018; Mora et al., 2014; Nieto-Veloza et al., 2021).

BAPs, which remain inactive within the parent protein, require careful extraction to unlock their full health-promoting potential (Sun et al., 2020). Enzymatic hydrolysis serves as a key method for releasing BAPs from their protein parent (Abachi et al., 2022). This process involves the addition of specific enzymes or utilizing enzymes produced through microbial fermentation to break down the protein structure and liberate the BAPs (Fig. 1). Solvent extraction offers another approach to separate BAPs from the protein matrix. In this method, proteins are dissolved in a suitable solvent, enabling the subsequent separation and concentration of the BAPs. However, the effectiveness of solvent extraction is limited by its relatively low extraction rate. This technique is typically reserved for specific types of polypeptides that exhibit specialized functions, such as β-defensins and P-insulin (Abachi et al., 2022; Kalenik et al., 2018). The enzymes used for enzymatic hydrolysis can be either extracted from natural sources such as plants and microorganisms or produced through recombinant DNA technology. Proteolytic enzymes such as trypsin (EC 3.4.21.4), pepsin (EC 3.4.23.1), and pancreatin (EC 3.4.21.70) are frequently employed in the enzymatic hydrolysis process. Additionally, microbial enzymes derived from sources like fungi, bacteria, and yeast, such as Alcalase (EC 3.4.21.62), and Flavourzyme (EC 3.4.11.1), are also widely utilized for BAPs hydrolysis. These enzymes offer specific proteolytic activities that can effectively break down proteins into BAPs fragments. The choice of enzyme depends on the specific protein substrate and the desired BAPs to be obtained, allowing for customized hydrolysis processes in BAPs research and development. The hydrolysis process can be carried out under controlled conditions of temperature, pH, and enzyme concentration to obtain BAPs with specific sequences and properties (Tsou et al., 2013). Moreover, several novel methods have also been developed to optimize the isolation of BAPs, such as subcritical water hydrolysis, chemical hydrolysis, ultrasound-assisted extraction, microwave-assisted extraction, and pulsed electric field processing (Costa et al., 2018; Franco et al., 2020; Ganeva et al., 2020). Meanwhile, in the food industry, production of BAPs by microbial fermentation offers its own benefits. This approach involves utilizing microorganisms like lactic acid bacteria and yeast to ferment food proteins, leading to the generation of BAPs. Through fermentation, not only are the bioavailability and biological activity of BAPs enhanced, but it also contributes to the enhancement of taste and texture in fermented foods (Chai et al., 2020). Once released, BAPs can be extracted and purified using various techniques such as ultrafiltration, ion-exchange chromatography, and reverse-phase high-performance liquid chromatography (Zou et al., 2022).

The efficacy of BAPs can vary depending on factors such as peptide sequence, dosage, and delivery method such as encapsulation to improve bioavailability and utilization (McClements, 2018). However, the efficacy can be increased by selecting appropriate protein source,

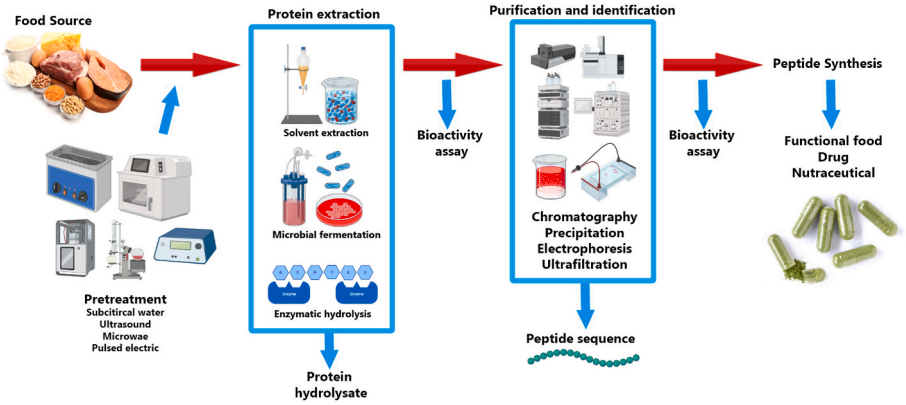

Fig. 1. BAPs production from food sources into health promoting products.

enzyme, hydrolysis conditions, and purification methods. *In vitro* and *in vivo* experiments are commonly used to investigate biological activities and potential health benefits of BAPs derived from food proteins (Ahn & Je, 2021; Grancieri et al., 2021; Oh et al., 2023). *In vitro* experiments serve as valuable tools for unraveling the intricate mechanisms underlying the action of BAPs. They provide crucial insights into how these bioactive compounds function at a molecular level. On the other hand, *in vivo* experiments offer a broader perspective by assessing the efficacy and safety of BAPs in living organisms. By combining the findings from both *in vitro* and *in vivo* studies, a more comprehensive understanding of the potential therapeutic applications of BAPs in treating obesity and related metabolic disorders can be attained.

3. Anti-obesity BAPs

BAPs derived from food proteins have multiple biological activities by targeting multiple pathways involved in the development of obesity and related metabolic disorders (Table 1). The multifaceted nature of BAPs positions them as promising alternatives for addressing obesity. Notably, BAPs are natural compounds known for their safety, tolerability, and minimal risk of adverse effects (Cao et al., 2021). BAPs can be obtained from a variety of food sources, including milk, eggs, fish, and soy, making them easily accessible and potentially more acceptable to consumers than traditional drugs. The gastrointestinal tract plays a critical role in the digestion and absorption of proteins and peptides (Jakubczyk et al., 2017). Proteolytic enzymes in the stomach such as pepsin unfolding their complex three-dimensional structure before move to the small intestine, where further digestion takes place (Ahn & Je, 2021). In the small intestine, pancreatic enzymes, including trypsin, chymotrypsin, and elastase, continue breaking down the peptides into even smaller peptide fragments and individual amino acids (Fan et al., 2018). These enzymes act on specific peptide bonds, further degrading the proteins into their building blocks. These smaller peptides and amino acids can be transported across the intestinal epithelium into the bloodstream, where they can be used for various physiological processes, including protein synthesis, energy production, and other cellular functions. The specific peptide sequences and their physicochemical properties influence their absorption and transport mechanisms (El et al., 2015).

BAPs can have different effects on the stomach and intestine. Some BAPs may be resistant to degradation and remain intact, exerting their bioactive effects directly in the stomach. These effects can include modulation of gastric acid secretion or regulation of appetite (Chungchunlam et al., 2023; Jakubczyk et al., 2017; Sharkey et al., 2020). In the intestine, BAPs can interact with various enzymes and receptors, influencing digestive processes and nutrient absorption (Baptista & Gigante, 2021). BAPs may enhance the activity of digestive enzymes, such as proteases, lipases, and carbohydrases, leading to improved protein, fat, and carbohydrate digestion (Sun et al., 2020). Additionally, BAPs can interact with intestinal receptors and transporters, affecting nutrient absorption and uptake. Furthermore, BAPs exert specific physiological effects in the intestine. They may modulate gut microbiota composition, promote the growth of beneficial bacteria, and inhibit the growth of harmful bacteria (Cao et al., 2019; R Costa et al., 2017; Shang et al., 2021). The gut microbiota has been implicated in the metabolism of protein hydrolysates. This interaction between protein hydrolysates and the gut microbiota highlights the potential for modulating the gut microbial composition and function through targeted interventions. BAPs can also have anti-inflammatory properties, helping to maintain gut health and reduce intestinal inflammation (Cao et al., 2019; R Costa et al., 2017).

3.1. Food-derived BAPs to prevent obesity

3.1.1. Milk proteins

Milk proteins are currently thought to be the most important sources of BAPs. These BAPs are released during the digestion of milk proteins such as casein and whey. They have been found to exhibit a range of biological activities, including satiety promotion, glucose regulation, and lipid metabolism modulation (Chungchunlam et al., 2023; Mudgil et al., 2018; Sharkey et al., 2020). Mudgil et al. (2018) have reported that nine novel BAPs derived from camel milk proteins are effective in suppressing key metabolic enzymes related to diabetes and obesity such as pancreatic α-amylase. Chakrabarti & Wu (2015) have found that two milk-derived peptides can induce beneficial adipogenic differentiation as evidenced by intracellular lipid accumulation, upregulation of PPARγ, and secretion of adiponectin, a protective lipid hormone, in 3T3-L1 preadipocytes (Chakrabarti & Wu, 2015). Alpha-lactalbumin, another milk-derived BAP, has been shown to be able to promote satiety and reduce food intake in humans (Chungchunlam et al., 2023; Kumar et al., 2022). This effect is believed to be due to alpha-lactalbumin's ability to increase the release of cholecystokinin (CCK), a satiety hormone, in the gut (Chungchunlam et al., 2023; Sharkey et al., 2020). Studies have shown that these peptides can stimulate the release of satiety hormones such as CCK and glucagon-like peptide-1 (GLP-1), which can reduce food intake and promote feelings of fullness (Kumar et al., 2022).

Fermented milk products such as yoghurt and kefir contain BAPs that are produced during the fermentation process. Potential anti-obesity effects of fermented milk products might be due to their ability to modulate gut microbiota, improve insulin sensitivity, and regulate appetite hormones (Manzanarez-Quin et al., 2023). Fermentation is one popular method for releasing BAPs from milk, it's not only extract peptide, but also give the benefit from bacteria secrete itself, and it produce unique sour taste (Chai et al., 2020). Fermented skimmed milk by *Enterococcus faecalis* and *Lactobacillus plantarum* can inhibit the differentiation of 3T3-L1 preadipocytes by lowering PPARγ expression and its target molecules such as adipocyte fatty acid-binding protein 2 (aP2), lipoprotein lipase (LPL), and resistin (Gil-Rodríguez & Beresford, 2019; Hassan et al., 2022; Hyun et al., 2021). Tumor necrosis factor alpha (TNF-α) is a cytokine involved in various physiological processes such as inflammation, apoptosis, and immune system regulation. It is thought to have various effects on adipogenesis. TNF-α can promote apoptosis of mature adipocytes and reduce mRNA levels of genes such as PPAR that are increased during adipogenesis. TNF-α expression is elevated by fermented skim milk, leading to suppression of adipocyte development in 3T3-L1 preadipocytes (Hyun et al., 2021). This finding is in line with results of a previous study evaluating anti-obesity effects of milk fermented by *Lactobacillus plantarum* NCDC 625 on high fat diet (HFD) fed C57BL/6J mice (Pothuraju et al., 2016).

Cheese is also a source of BAPs that have anti-obesity effects as fermentation and ripening processes of cheese can lead to formation of many different peptides (Baptista & Gigante, 2021; Yang et al., 2021). *Limosilactobacillus* spp. and *Lactiplantibacillus* spp. are lactic acid bacteria isolated from Mexican cheese that can produce anti-obesity fermented milk by inhibiting pancreatic lipase and lipid accumulation (Manzanarez-Quin et al., 2023). Whey protein-derived peptides present in cheese have been shown to have potential anti-obesity effects by increasing satiety and reducing food intake (Chungchunlam et al., 2023). Another report has shown that certain BAPs derived from cheese have anti-inflammatory and antioxidant effects, which may prevent obesity-related metabolic disorders (Yang et al., 2021). However, more research is needed to fully understand the potential anti-obesity effects of cheese-derived BAPs and to determine optimal amounts and types of cheese to consume for these effects.

3.1.2. Eggs

Eggs and some of their components including eggshell membrane, albumen, and yolk have long been acknowledged as high-value protein sources for humans. By providing the developing embryo with nutrients (proteins, lipids, vitamins, and minerals) as well as defense molecules, eggs and some of their components can help maintain a healthy and

Table 1
Anti-obesity bioactive peptides derived from foods.

Food source	Peptide name or sequence	Extraction methods	Evaluation and treatment model	Observed effects	Reference
Milk and dairy product					
Non-fat milk	Fermented milks (FMs)	Fermentation using LAB isolated from cheese	*In vitro* using 3T3-L1 preadipocyte, *in silico* digestion	Inhibit pancreatic lipase	Manzanarez-Quin et al. (2023)
Skim milk	LAB-fermented skimmed milk	Fermentation	*In vitro* using 3T3-L1 preadipocyte	Down-regulated PPARγ via the upregulation of the proinflammatory cytokine TNF-α	Hyun et al. (2021)
Human milk	AVPVQALLLNQ	Peptide identification through peptidomic, and synthesized	*In vivo* using HFD mice	Down-regulated PPARγ by sustaining ERK activity	Li et al. (2021)
Whey from bovine serum albumin	whey protein hydrolysate (WPH)	Enzymatic hydrolysis using pepsin -pancreatin	*In vitro* using 3T3-L1 preadipocyte and C2C12 myotubes	Upregulate PPARγ, increase adiposity	D'Souza et al. (2020)
Camel milk	FCLPLPLLK; KFQWGY; FMFFGPQ; MSKFLPLPLMFY; YWYPPK; YWYPPQ; LTMPQWW	Enzymatic hydrolysis using Alcalase	*In vitro* using enzymatic assay	Inhibit porcine pancreatic lipase, by binding into lipase binding site	Mudgil et al. (2018)
Milk	IPP and VPP	Enzymatic hydrolysis using protease peptide identification and synthesis	Murine 3T3-L1 preadipocyte	Upregulate PPARγ	Chakrabarti and Wu (2015)
Eggs					
Duck egg	VSEE	Enzyme hydrolysis using protamex (EC 3.4.21.)	*In vitro* using 3T3-L1 preadipocyte and *in vivo* using OVX rats' model	Increase Wnt/β-Catenin pathway related protein, activate RUNX2	Guo et al. (2019)
Chicken egg	Egg white hydrolysate (EWH), WEKAFKDED, QAMPFRVTEQE, ERYPIL, and VFKGL	Enzyme hydrolysis using pepsin	*In vitro* 3T3-L1 preadipocyte, *In vivo* using HFD rats	Upregulate PPARγ	Jahandideh et al., (2018)
Fish meat and Marine organism					
Shellfish(*Meretrix lusoria*)	*M. lusoria* protamex hydrolysate (MLPH)	Enzymatic hydrolysis using protamex	*In vivo* by ob/ob mice	Upregulate AMPK phosphorylation	Kim et al. (2022)
Ark shell	LLRLTDL, GYALPCDCL	Enzymatic hydrolysis using pepsin	*In vitro* murine MSC	Inhibit intracellular reactive oxygen species generation, increased cellular antioxidant enzyme activities, suppressed proinflammatory cytokine productions	(Ahn & Je (2021); Hyung et al. (2017))
Blue mussel	Blue mussel hydrolysate	Enzymatic hydrolysis using pepsin	*In vitro* using mouse MSC	Upregulate HO-1/Nrf2 pathway and down regulate adipogenesis transcription factor.	Oh et al. (2020)
Spirulina platensis protein	NALKCCHSCPA, LNNPSVCDCDCMMKAAR, NPVWKRK, CANPHELPNK	Enzymatic hydrolysis using trypsin, alcalase, pepsin, papain (EC 3.4.22.2) and protamex	*In vitro* using 3T3-L1 preadipocyte	Inhibit proliferation	Fan et al. (2018)
Shrimp shell waste	Shrimp shell waste hydrolysates (SSWH)	Enzymatic hydrolysis using neutrase, Alcalase, trypsin, papain and protamex	*In vitro* using enzymatic assay.	Inhibit α-amylase and posses antioxidant	Yuan et al. (2018)
Fish collagen	Subcritical water-hydrolyzed fish collagen peptide	Subcritical water-hydrolyzed	3T3-L1 preadipocyte and HFD mice.	Decrease expression of C/EBPα, PPARγ, and aP2 genes	Lee et al. (2017)
Yellow catfish	Yph	Enzymatic hydrolysis using Alcalase	In vivo by HFD mice	Modulate hepatic glucose enzyme and antioxidant activity	Kim et al. (2017)
Fish, wakame and other marine source	VW, VY, KY, KW, IY, AP, VIY, LKP, GPL, AKK and VAP	Enzymatic hydrolysis using trypsin, synthesis	Human white pre-adipocytes (HWP)	Down regulate of both PPARγ and C/EBPα expression	Henda et al. (2015)
Tuna	DIVDKIEI	Enzymatic hydrolysis using trypsin, synthesis	*In vitro* using 3T3-L1 preadipocyte	Activate the Wnt signaling pathway, inhibit C/EBPα expression	Kim et al. (2015)
Non-animal food source					
Chia seed (*Salvia hispanica* L.)	NSPGPHDVALDQ and RMVLPEYELLYE	Enzymatic hydrolysis using pepsin and pancreatin	*In vitro* using 3T3-L1 preadipocyte	Down regulate PPARγ, LPL, FAS, SREBP1, lipase activity and triglycerides	Grancieri et al. (2021)
Walnut protein	Walnut Meal Peptides (WMP)	Enzymatic hydrolysis using basic protease, neutral protease, papain, trypsin, pepsin and Alcalase.	*In vivo* by HFD rats	Down-regulate FAS and another adipogenesis related gene HMG-CoA reductase (HMGR), lecithin cholesterol acyltransferase (LCAT) and cholesterol 7α-hydroxylase (CYP7A1)	Yang et al. (2021)

(*continued on next page*)

Table 1 (*continued*)

Food source	Peptide name or sequence	Extraction methods	Evaluation and treatment model	Observed effects	Reference
Legume (black bean, green pea, chickpea, lentil and fava bean)	Legume protein hydrolysates (LPH), VNPDPAGGPTSGRAL, DLVLDVPS, KPSSAAGAVR, TKAGGTAF, VELVGPK	Enzymatic hydrolysis using Alcalase and pepsin/pancreatin	*In vitro* using enzymatic assay kit	inhibited pancreatic lipase and HMGR	Moreno et al. (2020)
Pea (*Pisum sativum* L.) Seed	Pea hydrolysates	Enzymatic hydrolysis using pancreatin	*In vitro* using 3T3-L1 preadipocyte	Promote adipocyte differentiation by increase PPARγ, aP2, induce GLUT4	Ruiz et al. (2020)
Hazelnut protein (*Corylus heterophylla* Fisch)	RLLPH	Enzymatic hydrolysis using pepsin	*In vitro* using 3T3-L1 preadipocyte	Downregulate expression level of mRNA related to adipogenesis and upregulate phosphorylated AMPK and its substrate ACC	Wang et al. (2020)
Quinoa (*Chenopodium quinoa* Willd.)	Quinoa protein hydrolysates FGVSEDIAEKLQAKQDERGNIVL, AEGGLTEVWDTQDQQF, YIEQGNGISGLMIPG, AVVKQAGEEGFEW, HGSDGNVF	Enzymatic hydrolysis using pepsin	*In vitro* using 3T3-L1 preadipocyte	Downregulate PPARγ, C/EBPα, aP2 and LPL expression levels	Shi et al. (2019)
Freshwater microalgae *Chlorella pyenoidose*	LLVVYPWTQR	Enzymatic hydrolysis using Alcalase.	*In vitro* using 3T3-L1 preadipocyte	Downregulate C/EBPα, SREBP-1c, AMPKα	Zhang et al. (2019)
Chickpea	VFVRN	Enzymatic hydrolysis using Alcalase.	*In vitro* using HepG2 cell and *In vivo* by HFD rats	Inhibit PPARγ, SREBP-1c, SREBP-2, FAS and HMGR	Shi et al. (2019)
Soybean	VHVV	Enzymatic hydrolysis using Flavourzyme®	*In vivo* by HFD mice.	Regulated TNF-α expression	Marthandam Asokan et al. (2018)
Phaseolus vulgaris	INEGSLLLPH,FVVAEQAGNEEGFE, SGGGGGGVAGAATASR, GSGGGGGGGFGGPRR, GGYQGGGYGGNSGGG YGNRG,GGSGGGGGSSSGRRP, GDTVTVEFDTFLSR	Microbial fermentation using L. *plantarum*	*In vitro* using enzymatic assay	Lipase inhibition	Jakubczyk et al. (2017)
Soybean	ILL, LLL, VHVV	Enzymatic hydrolysis using Flavourzyme®	*In vitro* using 3T3-L1 preadipocyte	Lipolysis-stimulating activity	Tsou et al. (2013)

well-balanced diet. Egg yolk-derived peptides have been found to exhibit anti-obesity effects through multiple mechanisms. For example, they have been shown to be able to reduce body weight gain by decreasing adipocyte size and inhibiting adipogenesis (Jahandideh et al., 2018). Egg yolk peptides have also been found to be able to improve lipid metabolism, including reducing plasma triglyceride and cholesterol levels, in animal models (Guo et al., 2019). Egg peptide can be prepared by enzymatic hydrolysis using enzymes such as thermolysin (EC 3.4.24.27) and pepsin to generate egg white hydrolysate (EWH). Previous studies have shown that EWH has anti-hypertensive effects by modulating renin angiotensin system (RAS) (Jahandideh et al., 2017). RAS contributes to the underlying pathophysiology of insulin resistance. Egg yolk-derived peptides, VSEE, have been shown to have potential anti-obesity effects by reducing body weight gain and improving lipid metabolism in animal models through modulation of Wnt/β-catenin signaling pathway (Guo et al., 2019; Jahandideh et al., 2019). However, for several peptides successfully sequenced, they act in opposite ways. From major egg white proteins ovalbumin and ovotransferrin, four peptides (WEKAFKDED, QAMPFRVTEQE, ERYPIL, and VFKGL) exhibit stimulatory effects on PPARγ and C/EBPα expression in murine 3T3-L1 preadipocytes (Jahandideh et al., 2017, Jahandideh et al., 2018). This might be related to the production of healthy adipocytes. Adipocytes under normal condition can release anti-inflammatory adipokine, such as adiponectin which is sensitive to insulin and inhibits differentiation of preadipocytes into mature adipocytes.

3.1.3. Fish and marine organisms

Fish and marine organisms are known to have a wide range of nutritional, functional, and biological properties. Fish muscle has a high amino acid content. It is a great source of nutritious and highly accessible proteins (Abachi et al., 2022). Numerous studies have revealed that fish protein hydrolysates have potential to control body weight or blood sugar levels, although these studies have not been able to definitively pinpoint the exact mechanism beneath this (Kim et al., 2017; Lee et al., 2017; Sharkey et al., 2020). In most papers, fish protein hydrolysates also have anti-hyperglycemic and satiating effects which might reduce calorie intake to prevent obesity (Sharkey et al., 2020). DIVDKIEI, a peptide sequence from boiled tuna, can inhibit C/EBPα and PPARγ expression levels by activating the Wnt/β-catenin pathway (Kim et al., 2015). Yellow catfish protein hydrolysate (YPh) modulate hepatic glucose enzyme with an antioxidant activity in HFD mice (Kim et al., 2017). After 84 days of taking different doses of YPh, mice showed significant improvements in all obesity-related complications. YPh treatment could also ameliorate hepatic steatosis by positively affecting hepatic glucose enzyme and antioxidant activities as well as pancreatic lipid digestive enzymes. Effects of 250 mg/kg YPh were found to be similar to or more effective than 10 mg/kg simvastatin (Kim et al., 2017).

Non-fish sources of marine proteins have also been explored. Various types of shellfish such as blue mussel and ark shell show strong anti-adipogenic effects. Successful characterization of marine-derived BAPs and investigations of their anti-adipogenesis effects support that shellfish show anti-adipogenic effect (Hyung et al., 2017; Oh et al., 2020). LLRLTDL and GYALPCDCL, two novel peptides derived from ark shell, can inhibit lipid accumulation by 48.53% and 46.22%, respectively, during adipocyte differentiation in mouse bone marrow-derived MSCs (Ahn & Je, 2021). Shellfish-derived peptide hydrolysates show anti-adipogenic effects on mouse MSCs by increasing lipolysis and reducing the expression of adipogenic transcription factors such as PPARγ, C/EBPα, and SREBP1 (Hyung et al., 2017; Oh et al., 2020). Kim et al. (2022) have reported the same result, showing an anti-obesity activity of protein hydrolysate of shellfish *Meretrix lusoria* (MLPH) through AMPK phosphorylation in obese mouse. After treatment with MLPH for six weeks, weights of the body and organs of mice were decreased and negative impacts of hepatic steatosis and epididymal fat were mitigated.

Fish processing industries generate a significant number of byproducts that are often underutilized or wasted. However, these byproducts can be valuable sources of BAPs known to possess various health-promoting properties, including anti-obesity effects. Hydrolysis of fish byproducts such as fish skin, bones, heads, and viscera can release BAPs with anti-adipogenic and lipid-lowering effects (Lee et al., 2017). Fish collagen peptide can inhibit adiposity by regulating specific markers. Lee et al. (2017) have reported that subcritical water-hydrolyzed fish collagen peptide (SWFCP) shows anti-obesity activity both *in vitro* and *in vivo*. SWFCP can downregulate master adipogenic transcription factors and the expression of a key adipogenic target gene in 3T3-L1 preadipocytes. An animal experiment model has shown consistent anti-obesity effects of SWFCP by suppressing mouse body weight (Lee et al., 2017). Marine byproducts such as seaweed and crustacean shells have also been found to contain BAPs with anti-obesity properties (Chaves Filho et al., 2020). A peptide derived from shrimp shell waste (SSWH) has been shown to be able to inhibit α-amylase, which will also inhibit the glucose uptake in intestine (Abachi et al., 2022). However, current marine peptides are still unable to match design specifications for medicines for obesity treatment due to their limited metabolic stability, low membrane permeability, and high manufacturing costs (Cao et al., 2021; Tak & Lee, 2021).

3.1.4. Non-animal food sources

Non-animal food source are good alternatives for those who are allergic to animal products and those who have decided to be vegetarians. Various plant-based sources such as fruits, vegetables, legumes, spices, edible flowers, mushrooms, and medicinal plants have demonstrated promising anti-obesity properties. Epidemiological studies have highlighted the beneficial effects of plant consumption in reducing the risk of obesity, while experimental studies have provided insights into the mechanisms underlying these effects (Lee et al., 2019). The mechanisms involve appetite suppression, inhibition of lipid and carbohydrate absorption, inhibition of adipogenesis and lipogenesis, regulation of lipid metabolism, increased energy expenditure, modulation of gut microbiota, and alleviation of obesity-related inflammation (Cao et al., 2019; Shang et al., 2021). Soy is the most popular alternative for non-animal derived peptide in obesity prevention through various mechanisms. Peptides derived from fermented soybean have been reported to possess anti-obesity activities through lipase inhibition, although their modulatory mechanisms associated with transcription factors have not been clearly defined (Jakubczyk et al., 2017). Tsou et al. (2013) have reported that soybean-derived peptides ILL, LLL, and VHVV exhibit lipolysis stimulating activity related to glycerol release in 3T3-L1 preadipocytes. In another study, Marthandam Asokan et al. (2018) have investigated *in vivo* effects of VHVV in HFD mice and observed changes in body weight, lipid levels, and suppression of TNF-α. Elevation of TNF-α during HFD treatment can lead to loss of muscle mass, development of insulin resistance, type 2 diabetes, and other metabolic disorders associated with obesity. Suppression of TNF-α expression by VHVV can increase energy uptake and lipid metabolism (Marthandam Asokan et al., 2018).

Hazelnut (*C. heterophylla* Fisch) derived peptides can inhibit adipogenesis by downregulating mRNA expression levels of several adipogenesis-related factors and enzymes such as PPARγ, C/EBPα, aP2, SREBP1, fatty acid synthase (FAS), acetyl-CoA carboxylase 1 (ACC1), and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) while upregulating levels of phosphorylated AMPK in 3T3-L1 preadipocytes (Wang et al., 2020). The peptide isolated and identified from black soybean (*Rhynchosia volubilis* Lour.) hydrolysate also has an adipogenesis inhibiting activity through phosphorylation of AMPK (Kim et al., 2007).

Other peptides derived from non-animal sources such as walnut, chickpea, quinoa, pea seeds, and chia seeds have been found to exhibit anti-obesity activity by inhibiting adipogenesis-related transcription factors (Grancieri et al., 2021; Ruiz et al., 2020; Shi et al., 2019; Yang et al., 2021). Legumes have also been shown to be able to inhibit pancreatic lipase and HMG-CoA reductase (HMGR), leading to suppression of cholesterol biosynthesis and serum lipoprotein levels (Moreno et al., 2020). A pentapeptide RLLPH derived from hazelnut can increase phosphorylated AMPK in 3T3-L1 preadipocytes. Elevation of phosphorylated AMPK can inhibit adipocyte differentiation by reducing the expression of key adipogenic transcription factors. Phosphorylated AMPK can also activate other signaling pathways involved in regulating adipogenesis, such as the Wnt signaling pathway (Wang et al., 2020). Microalgae are also considered as potential protein sources as alternatives of animal proteins. Besides, they possess several functional properties such as antioxidant, antihypertensive, and anti-cancer effects. Microalgae-derived peptides also possess anti-obesity effects. LLVVYPWTQR, a novel decapeptide from freshwater microalgae *Chlorella pyenoidose*, can inhibit lipid accumulation and fatty acid synthesis in 3T3-L1 preadipocytes by downregulating adipogenesis transcription factors such as PPARγ, C/EBPα, and SREBP-1c and decrease phosphorylated AMPK. This result is comparable to the commercial drug simvastatin (Zhang et al., 2019).

3.2. Mechanism of BAPs in modulating adiposity

BAPs can interact with intracellular proteins such as transcription factors involved in adipogenesis, lipid metabolism, and inflammation (Fig. 2) (Ahn & Je, 2021; Chakrabarti & Wu, 2015; Gil-Rodríguez & Beresford, 2019; Grancieri et al., 2021). By selectively targeting these interactions, BAPs may be able to modulate these cellular processes and ultimately lead to a reduction in adiposity. PPARs, SREBPs, and CEBPs are main transcription factors that play key roles in adipocyte differentiation, lipid metabolism, and insulin sensitivity (Kawai, 2013). BAPs can either activate or inhibit these transcription factors depending on the type and structure of the peptide. Most BAPs's anti-adipogenesis activity works by suppressing the expression level of PPARγ and its related signaling pathways (Grancieri et al., 2021; Hyun et al., 2021; Ruiz et al., 2020). As an example, BAPs from fish collagen is reported to inhibit adipogenesis both *in vitro* in 3T3-L1 preadipocytes and *in vivo* in HFD mice by down-regulating the expression of this transcription factor along with C/EBPα, and aP2 genes (Lee et al., 2017). The effect of modulation includes reduced number and size of adipocytes. This finding is in line with BAPs derived from skim milk (Hyun et al., 2021), chia seed (Grancieri et al., 2021), and chickpea (Shi et al., 2019). But conversely, in a report by Jahandideh et al. (2017), BAPs from egg white hydrolysate could promote the development of adipocytes by increasing PPARγ and C/EBPα expression. Elevated of adipocyte development is related to that fact that healthy adipocytes are insulin sensitive with an ability to secrete adiponectin, an anti-inflammatory hormone with benefits in preventing metabolic syndrome. Chakrabarti and Wu (2015) have reported similar results, where milk peptide can promote beneficial adipogenesis to prevent inflammation. These results show that the modulatory effect of BAPs (both inhibit or promote adipogenesis) is specifically dependent on the source and sequence of the amino acid that composes it.

BAPs can also modulate adiposity by regulating signaling pathways such as AMPK and mitogen-activated protein kinase (MAPK) pathways (Hou et al., 2020; Kawai, 2013). These pathways play important roles in regulating energy metabolism and inflammation in adipose tissues. BAPs can activate AMPK, leading to increased glucose uptake and fatty acid oxidation in adipocytes. Activation of AMPK has been hypothesized to imitate or exacerbate exercise-related effects such as fatty acid oxidation. Adipocyte development is inhibited by AMPK activation, which can also decrease the production of lipogenic molecules such FAS, ACC1, and PPARγ. As a result, activators of this enzyme could be used as therapeutic targets for obesity and obesity-related diseases such metabolic syndrome and type 2 diabetes (Ali et al., 2013; Takada et al., 2009), whereas inhibition of the MAPK pathway could lead to decreased expression of pro-inflammatory cytokines and improved insulin sensitivity.

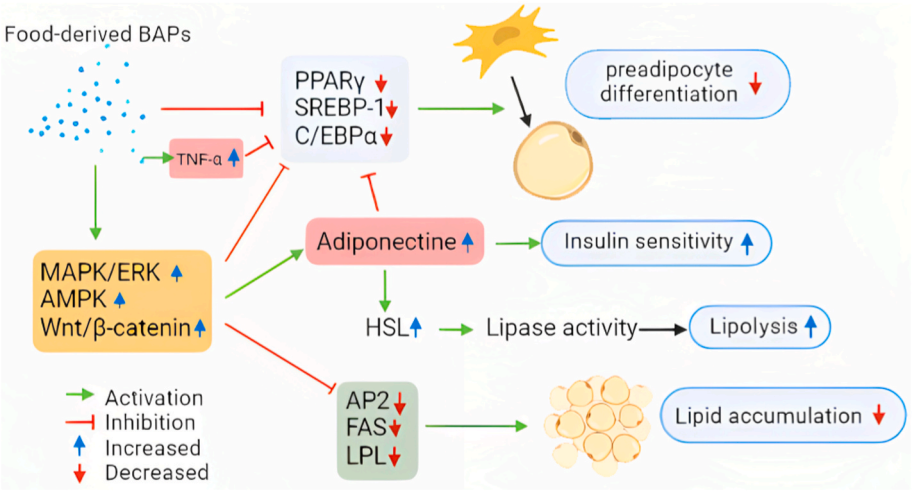

Fig. 2. Mechanisms of action for bioactive peptides as anti-obesity agents.

MAPK/extracellular signal-regulated kinase (ERK) pathway has been intensely investigated in adipocyte differentiation *in vitro* (Li et al., 2021; Ryu et al., 2010). ERK is required to initiate adipogenic differentiation process. However, it needs to be turned off to continue with adipocyte maturation. BAPs from human breast milk have been proven to be able to inhibit obesity through modulation of ERK1 which later will reduce PPARγ expression (Li et al., 2021). Pre-adipocytes can release TNF-α, whose expression reduces as adipogenesis develops. TNF-α can influences adipogenesis in a number of ways by promoting apoptosis in mature adipocytes and downregulating expression of adipogenesis-related genes including PPARγ. BAPs from fermented skim milk and soybean can upregulate proinflammatory cytokine TNF-α in 3T3-L1 preadipocyte which then inhibit the expression of PPARγ (Hyun et al., 2021; Marthandam Asokan et al., 2018). While inhibiting adipogenesis can be beneficial in some cases, chronic elevation of TNF-alpha is associated with inflammation, which is known to promote metabolic dysfunction and the development of obesity-related diseases such as insulin resistance, type 2 diabetes, and cardiovascular disease. Wnt/β-catenin signaling pathway is also a target for BAPs anti-adipogenesis activity (Kawai, 2013). BAPs may affect this pathway by interacting with the extracellular domain of Frizzled receptors, which are transmembrane receptors that can bind to Wnt ligands and activate the Wnt/β-catenin signaling pathway (Hou et al., 2020). BAPs from duck egg can increase the accumulation of Wnt which can then stabilize β-catenin, followed by cascade that can regulate lipid metabolism by decreasing PPARγ, an adipocyte translation factor. This signaling pathway will increase key osteogenic transcription factors (RUNX2) in the same time (Guo et al., 2019).

Furthermore, BAPs can modulate adiposity by regulating adipokine secretion and adipose tissue inflammation. Adipokines are secreted by adipocytes. They play important roles in energy metabolism and inflammation. BAPs can regulate the secretion of adipokines such as adiponectin, leptin, and resistin, which can improve insulin sensitivity and reduce adipose tissue inflammation (Chakrabarti & Wu, 2015; Grancieri et al., 2021).

4. Industrial application and challenge

The use of BAPs as a natural ingredient in food products is an attractive strategy to provide a safe and effective approach to prevent and treat obesity (Johnson et al., 2022). Since BAPs are small molecules, contrived BAPs can target specific protein interactions effectively (Cao et al., 2021; Tsomaia, 2015). Additionally, BAPs exhibit a broad range of therapeutic effects with low levels of toxicity and structural diversity without accumulation or with very little accumulation in bodily tissues. Thus, it is very understandable that the pharmaceutical industry is continuously searching for and developing treatment based on BAPs (Cao et al., 2021). A therapeutic peptide can be generated to address a specific problem using either biological techniques or chemical synthesis. In some conditions, a combination of these two might be employed. (Zou et al., 2022). However, laboratory synthesis is the most reasonable way in industrial application since it allows access to all sequences and insertion of biochemical and biophysical probes that cannot be produced via biological processes, such as synthetic amino acids or building blocks. It also needs shorter time compared to traditional BAPs isolation from raw food. Several known synthetic methods such as solution-phase synthesis, solid-phase synthesis, and polymerization methods have been developed (Zou et al., 2022). The development of cost-effective and scalable production methods will enhance the potential of BAPs for commercialization in food and pharmaceutical industries.

Most BAPs-based treatments are progressing into clinical trials for the treatment of metabolic diseases. These trials involve the use of human subjects. They are conducted in several phases, starting with small-scale safety studies and moving onto larger-scale efficacy studies. The average number of peptide therapies receiving clinical investigations has increased exponentially during the past three decades (Cao et al., 2021; Shi et al., 2022; Tsomaia, 2015). The efficacy of using BAPs as a replacement for chemical medications has been questioned. However, studies have proven that it is at least as effective as commercially available pharmaceuticals or even higher (Shi et al., 2022).

The accessibility of BAPs source is actually high and sustainable. Any food product could be used to produce therapeutic BAPs, although protein-rich foods are preferred (Johnson et al., 2022). The production of BAPs can also use waste materials from companies that process food, which can reduce the cost of raw materials. However, BAPs face certain challenges that need to be addressed in order to realize their therapeutic potential, including the potential to trigger a systemic immune response before reaching their intended therapeutic targets (especially with prolonged administration) and difficulty to reach intracellular targets (Cao et al., 2021). BAPs need to reach their target sites within the body to exert their intended effects. However, they may face challenges in terms of bioavailability, which refers to their ability to be effectively absorbed, distributed, and retained in the body. Specialized delivery techniques such as peptide encapsulation with micro- and nano-sized polymers or particles like dendrimers, liposomes, and polyectrolyte microspheres can overcome this challenge (McClements, 2018). Encapsulation can help protect peptides from enzymatic degradation in the stomach (R Costa et al., 2017). *In vitro* and *in vivo* experiments have

been carried out to evaluate the bioavailability of peptides. The potential of BAPs's bioactivity following gastrointestinal digestion may initially be determined using *in vitro* experiments, allowing the highest potential samples to be examined *in vivo*. These peptides could be appropriate for *in vivo* research to verify earlier findings and determine if bioactivity assessed could be maintained (Li et al., 2021).

Practical limitations in the context of applying BAPs refer to challenges or constraints that arise during their practical implementation or use in various applications. These limitations can affect factors such as production, administration, and overall feasibility. The production of BAPs may involve complex processes, including extraction, purification, and synthesis (Cao et al., 2021). These processes can be time-consuming, costly, and require specialized equipment and expertise. The limitations may arise in scaling up production to meet demand or achieving consistent and cost-effective production methods. Another limitation is stability and storage. BAPs can be sensitive to environmental conditions such as temperature, pH, and light. Maintaining their stability during storage and transportation can be challenging. This limitation may include finding suitable storage conditions, developing effective preservation methods, or addressing issues related to degradation or loss of activity over time.

Regulatory considerations play a crucial role in the application of BAPs in medical or food-related contexts. Adhering to regulatory standards and obtaining necessary approvals are essential steps in bringing BAPs to the market. Navigating complex regulatory frameworks, meeting safety and efficacy requirements, and fulfilling documentation and approval procedures are practical limitations that need to be addressed. Collaboration between researchers, regulatory authorities, and industry stakeholders is crucial to ensure compliance and facilitate the practical implementation of BAPs.

Another important practical aspect to consider is the cost-effectiveness of BAPs. While the therapeutic potential of BAPs is promising, their practical application should be economically viable and accessible to a broader population. Cost considerations arise at various stages, including large-scale production, formulation, and delivery systems. Developing cost-effective processes and strategies for BAP production and ensuring affordable pricing are key factors to maximize the impact of BAPs in managing obesity and related conditions. Balancing the effectiveness of BAPs with their affordability is an important practical consideration for their widespread adoption and availability.

Addressing regulatory considerations and optimizing cost-effectiveness are essential steps in translating the potential of BAPs into practical solutions for obesity management. Collaboration among researchers, regulatory agencies, industry stakeholders, and healthcare providers can facilitate the development of a supportive ecosystem for the practical implementation of BAPs. By addressing these practical aspects, the utilization of BAPs in medical and food-related applications can be streamlined, ensuring their accessibility, safety, and affordability for the benefit of individuals affected by obesity.

5. Future prospect and further research

5.1. Targeted therapies

Intracellular protein interactions regulate a number of crucial cellular processes linked to human diseases (Hou et al., 2020; Zhao et al., 2022). This interaction is potential as therapy target. Future research may uncover specific compounds with well-defined mechanisms of action that can target key pathways involved in obesity. Some compounds can specifically inhibit the interaction or enhance it and exhibit therapeutic activity. Understanding these mechanism provides a new idea for the exploration and development of treatment methods for obesity (Hou et al., 2020). Another promising approach for future use of BAPs as anti-obesity agents is the use of combination therapies. By combining multiple BAPs that target different aspects of adipogenesis and lipid metabolism, it may be possible to achieve synergistic effects and improve overall therapeutic efficacy (Tsomaia, 2015). Current scientific progress and new study areas such as epigenetics are expected to explain the complex mechanisms involved in MSCs differentiation known to generate innovative MSC-based treatment approaches for obesity (Cao et al., 2021; Lee et al., 2019). Although these processes are not completely understood, several of these growth factors are known to induce an "inverse connection" between adipogenic and another lineage development such as bone and muscle. Food protein derived BAPs have been shown to possess a modulatory effect on one and another differentiation lineage and cell growth by upregulating several signaling pathways. The discovery of novel target genes related to adiposity is also still a wide-open field to be revealed in order to get a more effective therapy. This could lead to the development of targeted therapies that modulate appetite, lipid metabolism, energy expenditure, or adipogenesis, offering more precise and effective treatment options.

5.2. The development of computational modelling

Advances in protein-protein interaction screening techniques, have made it easier to identify potential intracellular protein targets for BAPs. Advances in computational modeling and simulation techniques have allowed for rational design of BAPs with improved specificity (Cian et al., 2022). It offers efficiency by enabling the exploration of various scenarios and hypotheses in a shorter timeframe. Cost-effectiveness is achieved through reduced reliance on extensive experimental studies. Accessibility has increased as user-friendly software becomes available. Molecular interactions between BAPs and target proteins can be predicted, aiding rational design. Computational modeling also facilitates property prediction, optimization, and exploration of a large chemical space, leading to accelerated drug discovery. These advantages contribute to the progress and potential of computational modeling in advancing BAP-based therapies for obesity. One notable study by Ruiz-López et al. (2023) utilized molecular docking simulations to investigate the binding interactions between BAPs derived from rice (*Oryza sativa*) and PPARγ. The study revealed strong binding affinity and favorable interactions between the BAPs and the receptor, suggesting its potential as an anti-adipogenic factor targeting PPARγ since it is a key regulator of adipogenesis. Previously, Ye et al. (2006) also reported PPARγ antagonist peptide using molecular docking. Advancements in software development have also played a crucial role in facilitating computational modeling studies. The development of user-friendly and robust software tools, such as AutoDock Vina (Trott & Olson, 2010), has made molecular docking simulations more accessible to researchers, enabling the screening and evaluation of a vast library of BAPs against target proteins relevant to obesity.

5.3. Improved bioavailability and delivery systems

Bioavailability and effective delivery of bioactive compounds are crucial for their therapeutic efficacy (Cao et al., 2021). A deeper comprehension of the biology of peptides and the development of novel peptide synthesis methods are needed to generated more challenging and complex peptides using the inventory of innovative chemicals and the upgraded technology and equipment. The development *in vitro* method such as the infogest protocol, a standardized *in vitro* digestion model, has emerged as a valuable tool in this context. Using this protocol, El et al. (2015) revealed the release, stability, and absorption patterns of goat milk and kefir, and found that after digestion the BAPs formed has higher inhibitory effect on α-amylase compared to undigested samples. This protocol, combined with other research approaches, offers a valuable platform for investigating the impact of formulation strategies, delivery systems, and food matrices on the bioavailability of BAPs (Johnson et al., 2022; Tsomaia, 2015). More crucially, they could support the scaled up for industrial production. Main goals of improvement are reduction of production costs and development of reproducible techniques that will create high-quality

end products.

5.4. Public acceptance

As research progresses, there is the potential for the clinical translation of BAPs as approved treatments for obesity (Cao et al., 2021). This would involve rigorous clinical trials, regulatory approvals, and integration into healthcare practices, offering healthcare providers additional tools to combat obesity and its associated health risks. It's important to note that public acceptance may evolve over time as more research is conducted, and as BAPs become more recognized and understood in the scientific and medical communities. The perception of safety and efficacy is crucial in determining public acceptance (Johnson et al., 2022). Extensive research and clinical studies demonstrating the safety and effectiveness of BAPs can contribute to increased public acceptance. Official regulatory approvals from health authorities can instill confidence in the public regarding the use of BAPs. When regulatory bodies assess and approve BAPs for therapeutic purposes, it can enhance public trust and acceptance. Clear and transparent communication about the benefits, risks, and limitations of BAPs is essential in shaping public perception. Open dialogue between researchers, healthcare professionals, regulatory bodies, and the public can help address concerns and provide accurate information.

Public acceptance can also be influenced by cultural and societal factors. Attitudes towards novel therapies, alternative medicine, and dietary supplements may vary among different cultures and communities.

6. Conclusion

It's important to note that while the future outlook for using BAPs as anti-obesity treatment appears promising, further research, validation, and clinical studies are needed to fully establish their safety, efficacy, and practical application. The development and utilization of BAPs as a mainstream anti-obesity therapy will require ongoing scientific advancements, regulatory considerations, and collaborative efforts between researchers, clinicians, and industry stakeholders.

Author contributions

I.T.S.: Writing-original draft, Writing-review & editing. **J.Y.J.**: Conceptualization, Writing-review & editing. Funding acquisition.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tifs.2023.06.015.

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