Chinese Journal of Natural Medicines

Recent advances, strategies, and future perspectives of peptide-based drugs in clinical applications

Qimeng Yang, Zhipeng Hu, Hongyu Jiang, Jialing Wang, Han Han, Wei Shi, Hai Qian

Citation: Qimeng Yang, Zhipeng Hu, Hongyu Jiang, Jialing Wang, Han Han, Wei Shi, Hai Qian, Recent advances, strategies, and future perspectives of peptide-based drugs in clinical applications, Chinese Journal of Natural Medicines, 2025, 23(1), 31-42. doi: 10.1016/S1875-5364(25)60800-4.

View online: https://doi.org/10.1016/S1875-5364(25)60800-4

Chinese Journal of Natural Medicines 23 (2025) 31-42

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Recent advances, strategies, and future perspectives of peptide-based drugs in clinical applications

Qimeng Yang[a,Δ], Zhipeng Hu[a,Δ], Hongyu Jiang[a], Jialing Wang[a], Han Han[a,*], Wei Shi[a,*], Hai Qian[a,b,*]

[a] *Centre of Drug Discovery, State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China*
[b] *Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease, China Pharmaceutical University, Nanjing 210009, China*

ARTICLE INFO

Article history:
Received 7 July 2024
Revised 15 August 2024
Accepted 1 September 2024
Available online 20 January 2025

Keywords:
Peptide-based drugs
Oncology
Diabetes
Antimicrobial peptides
Neurodegenerative diseases

ABSTRACT

Peptide-based therapies have attracted considerable interest in the treatment of cancer, diabetes, bacterial infections, and neurodegenerative diseases due to their promising therapeutic properties and enhanced safety profiles. This review provides a comprehensive overview of the major trends in peptide drug discovery and development, emphasizing preclinical strategies aimed at improving peptide stability, specificity, and pharmacokinetic properties. It assesses the current applications and challenges of peptide-based drugs in these diseases, illustrating the pharmaceutical areas where peptide-based drugs demonstrate significant potential. Furthermore, this review analyzes the obstacles that must be overcome in the future, aiming to provide valuable insights and references for the continued advancement of peptide-based drugs.

1. Introduction

Peptides are versatile molecules that possess a wide range of biological functions and therapeutic potential. Comprising amino acids connected by peptide bonds, peptides exhibit unique sequences and structures [1]. Since the initial therapeutic application of insulin in 1922, peptide-based drugs have undergone a century of development. This evolution has highlighted the increasing importance of peptides due to their specificity and efficacy in treating various diseases, ranging from metabolic disorders to cancers [2]. Frost & Sullivan predicts that the global market for peptide-based therapies will expand from USD 62.8 billion in 2020 to USD 96 billion in 2025, with the Chinese market growing from USD 8.5 billion to USD 18.2 billion during the same period. The projected compound annual growth rates (CAGRs) for the China and global markets are 16.4% and 8.9%, respectively [3]. Notably, Novo Nordisk's Semaglutide achieved global sales of USD 10.914 billion in 2022, securing the top position, followed by Lilly's Dulaglutide with sales of USD 7.44 billion [4]. In the first three quarters of 2023, Semaglutide sales increased by 49% year-on-year, reaching USD 14.232 billion, while Tirzoptide, launched in May 2022, generated sales of USD 2.958 billion during the same period [5]. These data underscore the rapid growth and immense potential of the peptide-based drug market, emphasizing the significance and growth momentum of such drugs worldwide. The increasing efficacy and market demand for peptide-based drugs indicate that further research and innovation in this field will likely lead to the development of more effective treatment options for a wide range of diseases.

As of now, approximately 120 peptide-based drugs have received international regulatory approval, primarily addressing therapeutic areas, such as rare diseases, oncology, diabetes, gastrointestinal disorders, immunological conditions, and cardiovascular diseases (Table S1). The leading peptide-based therapeutics by market share are anticancer, endocrine, and metabolic drugs, each accounting for 17% of total sales. Recent approvals, particularly of glucagon-like peptide-1 (GLP-1) receptor agonists for metabolic disorders, have elevated cancer and metabolic therapies in sales rankings [2, 6]. Furthermore, research on peptide-based treatments for antibacterial and neurodegenerative diseases has seen rapid advancements. Therefore, a comprehensive review of the applications of peptide-based therapeutics across these diseases is imperative.

Despite the expanding application of peptides in biomedical fields, several inherent limitations continue to hinder their therapeutic efficacy, including poor oral bioavailability, short plasma half-life, susceptibility to proteolytic degradation, and restricted tissue penetration [7-9]. To overcome these challenges, extensive research has focused on structural modifications of peptides, such as backbone remodeling, lipidation, polyethylene glycol (PEG) conjugation, and protein fusion, which have collectively enhanced their stability, bioavailability, and therapeutic efficacy [10-15]. Furthermore, peptides have gained prominence as carrier materials in nanoparticle drug delivery systems, such as peptide self-assembly systems [16-19], capitalizing on their intrinsic biocompat-

* Corresponding author.
E-mail addresses: hhan_cpu2017@163.com (H. Han); shiwei@cpu.edu.cn (W. Shi); qianhai24@163.com (H. Qian)
Δ These authors contributed equally to this work.

https://doi.org/10.1016/S1875-5364(25)60800-4

ibility and biodegradability for efficient drug encapsulation and targeted delivery. These advancements show great potential for treating complex diseases like cancer and further broaden the market prospects for peptide-based therapeutics.

This review focuses on the transformative applications of peptide-based drugs in the pharmaceutical field, with a particular emphasis on recent research advancements in oncology, diabetes, antimicrobial treatments, and neurodegenerative diseases. Furthermore, it provides a comprehensive overview of typical peptide-based drugs in preclinical and clinical studies, systematically examining their applications and current challenges across various diseases. Finally, this review analyzes and anticipates future directions for peptide-based drug modification and research, presenting a range of prospective strategies.

2. Synthesis of peptide-based drugs

Peptide synthesis involves two fundamental methods: chemical synthesis and biological synthesis. Chemical synthesis techniques, including solid-phase peptide synthesis (SPPS) and liquid-phase peptide synthesis (LPPS), create peptide sequences through dehydration condensation reactions between amino acids. However, due to the presence of additional functional groups in amino acids, it is necessary to temporarily protect these non-participating functional groups to ensure the correct synthesis of the intended peptide product. Biological synthesis methods encompass fermentation and enzymatic hydrolysis [6]. With advancements in biotechnology, genetic engineering approaches, primarily based on DNA recombination technology, have been employed for peptide synthesis (Fig. 1).

2.1. Chemical synthesis

2.1.1. SPPS

SPPS, developed by Merrifield in 1963, is based on anchoring the *C*-terminus of the first amino acid to a solid support resin. The *N*-terminus of this amino acid is protected by a protecting group [20]. Peptide chain elongation occurs through iterative cycles of protecting group removal and coupling with an excess of the next activated amino acid derivative. Upon completion of the target peptide chain assembly, it is cleaved from the resin, then isolated, and purified. The choice of protecting groups is critical in SPPS, with the two most common being the Boc group, introduced by Merrifield, and the Fmoc group, introduced by Carpino. The Fmoc group, which offers superior acid stability, minimizes side reactions and enhances synthesis efficiency, making it the preferred method in modern peptide synthesis. SPPS is advantageous for its precise control over peptide chain length, suitability for large-scale production, and compatibility with automated, high-throughput peptide synthesis. However, this process requires an excess of amino acids and coupling agents, resulting in substantial consumption of raw materials and increased production costs [21].

2.1.2. LPPS

LPPS, initially proposed by Bayer and Mutter in 1972, shares a fundamental principle with SPPS. However, the primary distinction lies in the replacement of the solid-phase resin with soluble reagents that link to the *C*-terminus of the first amino acid [22]. LPPS primarily divides into two strategies: stepwise synthesis and fragment condensation. Stepwise synthesis is straightforward and rapid, suitable for synthesizing various biologically active peptide segments. Fragment condensation methods mainly include native chemical ligation and Staudinger ligation. In recent years, LPPS fragment synthesis has rapidly advanced, achieving significant breakthroughs in the synthesis of peptides and proteins. Compared with SPPS, LPPS offers the advantage of eliminating the need for repeated washes, thereby reducing reagent use, lowering costs, and enhancing environmental sustainability. However, it suffers from low synthesis efficiency and complex purification steps [22].

2.2. Biosynthesis of peptides

2.2.1. Enzymatic hydrolysis

Enzymatic hydrolysis represents a specialized technique for peptide preparation. The process involves the hydrolysis of proteins at specific amino acid sites using particular proteases, such as alkaline protease and trypsin, resulting in peptide products. In both laboratory research and commercial production, enzymatic hydrolysis is primarily employed to generate biologically active peptides derived from food sources, including nut peptides and milk peptides. Laboratory studies have demonstrated that peptides produced *via* enzymatic hydrolysis exhibit biological functions such as antioxidant activity and blood pressure reduction. However, in commercial production, enzymatic hydrolysis is primarily employed in the production of medical nutrition products and nutraceuticals. Therefore, its application in manufacturing pharmaceutical-grade is limited [23,24].

2.2.2. Microbial fermentation

Microbial fermentation is another method used for the production of bioactive peptides through the metabolic processes of microorganisms. Antihypertensive peptides, for instance, can be derived from the fermentation products of *Lactobacillus helveticus* and *Lactobacillus acidophilus*. However, this approach is inher-

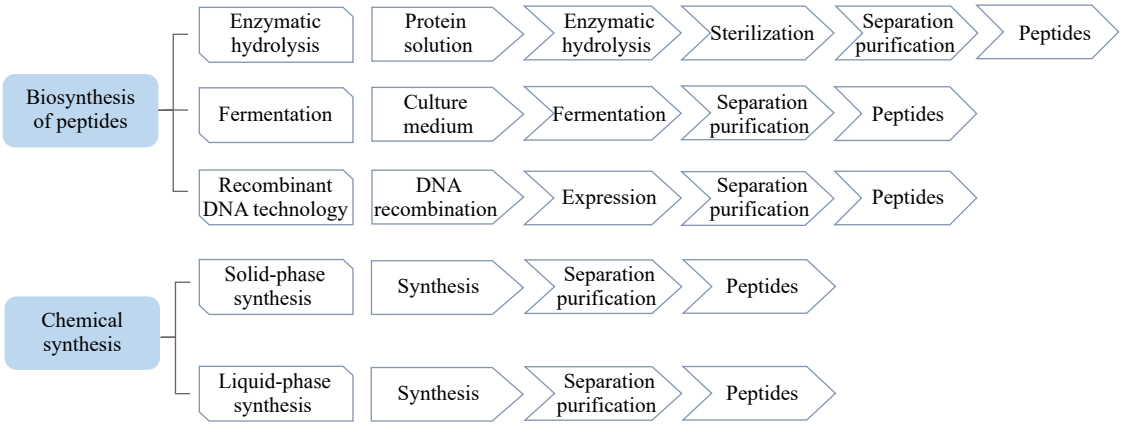

Fig. 1 Synthesis method of polypeptide.

ently limited to peptides that the microorganisms can produce, restricting its scope to compounds with biological functions. Consequently, microbial fermentation is not widely employed as a method for the production of peptide-based drugs [25].

2.2.3. Recombinant DNA technology

Since its initial application in the production of human insulin in 1982 [26], recombinant DNA technology has been extensively utilized in the manufacture of peptide-based drugs. This approach involves two primary stages: the design and amplification of a gene fragment encoding the target peptide, followed by the expression of this gene fragment within a host cell. Microorganisms serve as the primary host cells in recombinant DNA technology. Compared with SPPS and LPPS, recombinant DNA technology provides the benefits of reduced production costs and enhanced efficiency, finding commercial applications in the realms of peptide antibiotics, interferons, and human hormones [27]. However, when contrasted with chemical synthesis methods, recombinant DNA technology presents challenges such as an increased occurrence of by-products and more complex product purification processes (Table S2).

3. Peptides in oncology

Cancer remains one of the most challenging diseases to treat, with current therapies often limited by issues such as non-specificity, toxicity, and poor bioavailability. In recent years, peptides have emerged as a focal point in cancer research due to their molecular specificity, favorable safety profile, and improved bioavailability. These properties enable peptides to function effectively in targeted therapy, immune regulation, and drug delivery for tumors. Therefore, peptide-based drugs hold immense potential to revolutionize cancer treatment strategies.

3.1. Anticancer peptides (ACPs)

ACPs have garnered significant attention in the field of antitumor therapy, propelled by advancements in molecular biology. These peptides specifically target cancer cells through various mechanisms while minimizing collateral damage to healthy cells [28]. ACPs exert their effects by inducing apoptosis, disrupting cellular membranes, inhibiting angiogenesis, and modulating signaling pathways. Moreover, these peptides possess the ability to disrupt crucial signaling pathways that support the survival, proliferation, and metastatic potential of cancer cells. By targeting and regulating proteins involved in cell cycle regulation, growth factor signaling, or survival pathways, ACPs effectively suppress cancer cell growth and survival [29, 30]. As of 2022, the Food and Drug Administration (FDA) and EMA have approved more than 20 ACPs for clinical use [31].

Despite the potential of cationic peptides, their therapeutic efficacy is often hindered by drawbacks such as high toxicity and inadequate targeting. Consequently, a primary focus of research in this field is the efficient modification or reconstruction of ACPs to enhance their targeted therapeutic performance while minimizing toxicity [32, 33]. For instance, Li et al. developed a VEGFR-3 homing peptide library using computational design. The overlap between positive immunostaining and VEGFR-3 expression confirmed the high affinity and selectivity of a novel peptide, CP-7. This finding suggests that CP-7 is a promising homing peptide for VEGFR-3-positive cancers *in vitro* and *in vivo*, with the potential to facilitate efficient drug delivery [34]. In another study, Setrerrahmane et al. successfully synthesized bifunctional peptides by combining HM-3 and AP25, which target αvβ3 and α5β1 integrins, respectively, using recombinant DNA technology in *E. coli*. The results demonstrated promising antiangiogenic and antiproliferative effects *in vitro*, particularly enhancing activity against gastric cancer cells while maintaining safety profiles in normal cells [35]. Furthermore, Li et al. engineered a novel fusion protein, LMRAP, by combining a GnRH-Fc fragment with the integrin-targeting AP25 anti-tumor peptide. Experimental data revealed that the LMRAP fusion protein maintained the function of GnRH receptor blockade, exhibited antiangiogenic properties, and displayed favorable tolerance and extended half-life [36].

In summary, the optimization of ACPs through various strategies can further reduce toxicity while enhancing targeting ability and therapeutic efficacy, ultimately maintaining their anticancer activity. These studies have established a foundation for the clinical application of ACPs; however, they have not provided novel research ideas for the development of safer and more effective ACPs.

3.2. Peptides in tumor immunization

Immunotherapy-based cancer treatments have been extensively investigated since 1890 [37]. The primary mechanism of cancer immunotherapy involves the reactivation of anti-tumor immune responses mediated by various immune cells, effectively countering tumor immune evasion [38]. Immune checkpoint inhibitors (ICIs) represent one of the most advanced forms of immunotherapy. The FDA and the National Medical Products Administration (NMPA) in China have approved antibodies that target immunological checkpoints, such as programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies, for the treatment of a wide range of cancers, resulting in favorable clinical outcomes (Fig. 2).

However, the large molecular size of antibodies often hinders their tumor penetration, limiting their clinical applications. Conversely, peptides possess the ability to infiltrate tumors and inhibit PD-1/PD-L1 interactions within the tumor microenvironment [39]. For instance, Miao et al. developed JMPDP-027, an optimized cyclic peptide that demonstrated T-cell reactivation capabilities comparable to pembrolizumab, an anti-PD-1 monoclonal antibody, and effectively disrupted PD-1/PD-L1 protein-protein interactions [40]. Similarly, Tao et al. employed phage display to identify P-F4, a PD-1-targeting peptide that modulated T-cell activity *in vitro* and inhibited the PD-1/PD-L1 interaction at the cellular level [41]. These studies further exemplify the immense potential of peptides as immune checkpoint inhibitors in anticancer therapy. The high specificity, adaptability, ease of production and modification, and minimal side effects of peptides render them a highly promising immunotherapy approach. As research and development of peptide immune checkpoint inhibitors progress, they are anticipated to assume a more pivotal role in cancer treatment in the future.

An alternative approach in tumor immunotherapy involves utilizing peptides as antigens to stimulate immune responses and activate antigen-presenting cells (APCs). This process encompasses several critical stages: 1) Antigen recognition: tumor cells express tumor-associated antigens (TAAs) or neoantigens, which

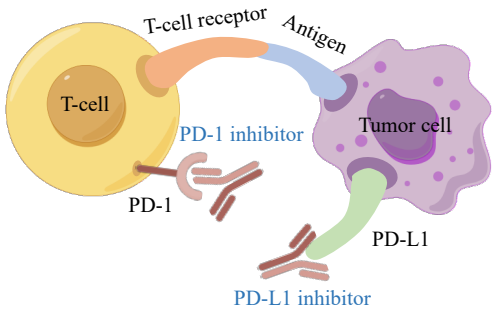

Fig. 2 Mechanism diagram of PD-1 immunotherapy.

are recognized as "non-self". 2) Antigen presentation: APCs, including dendritic cells, macrophages, or B cells, internalize and process peptide antigens. These antigens are then displayed on their surface, bound to major histocompatibility complex (MHC) molecules. 3) Cell activation: T-cell receptors (TCRs) recognize the presented antigen, leading to T-cell activation and the initiation of an immune response targeting tumor cells [42-44]. However, when designing such peptides, it is crucial to ensure the immunogenicity of the peptide antigens while simultaneously avoiding autoimmune responses. Moreover, the stability of peptide antigens *in vivo* and their efficient delivery to APCs rely on effective delivery methods. For instance, Shi et al. employed docking techniques to model the interaction between HLA-A2 and MAGE-1p230-238, elucidating the structure-activity relationship of tumor-associated antigen peptides. They engineered several novel tumor antigen peptides using SAYGEPRKL (MAGE-1p230-238) as a lead compound. Among these, peptide I-6 exhibited a high affinity for HLA-A2 and elicited a potent, targeted immune response in $CD8^+$ T cells both *in vivo* and *in vitro* [45]. This research presents a novel strategy to enhance the anti-tumor efficacy of antigenic peptides by increasing the affinity between peptides and presentation molecules, offering a practical, straightforward, and safe approach to cancer immunotherapy.

3.3. Peptide-drug co-delivery

In recent years, peptide-drug co-delivery has demonstrated significant potential in drug delivery and anticancer treatment. The primary approaches include peptide-drug conjugates (PDCs), physical encapsulation of peptides and drug molecules, and peptide-mediated co-assembly with drug molecules [46-49]. While each of these technologies has its own merits and limitations, they collectively enhance drug delivery efficiency, improve targeting in cancer treatment, minimize side effects, and ultimately increase the overall efficacy of the treatment (Fig. 3).

3.3.1. PDCs

PDCs are emerging as one of the most promising conjugate medicines following the development of antibody-drug conjugates (ADCs) [50]. PDCs are formed when a drug is covalently linked to a functional peptide sequence through a unique linker, consisting of three primary components: the drug, the peptide, and the linker (Fig. 4). Initially, PDCs achieve targeted distribution to specific regions through peptide-mediated active or passive targeting. Subsequently, they effectively deliver the PDCs into cells *via* cell-penetrating peptides or receptor-mediated translocation [51]. Finally, to exert the therapeutic effect, the linkers cleave specifically in response to environmental cues or enzymatic action, releasing the active payload [52]. Furthermore, PDCs are also commonly used as imaging agents, utilizing radionuclides instead of hazardous compounds as the payload. These PDCs can perform imaging or therapeutic functions using various radionuclides, with some radionuclides possessing the ability to fulfill both roles. For example, 111In-DTPA-octreotide was the first radionuclide-containing PDC approved by the FDA [53].

In comparison with conventional chemotherapy agents, PDCs have demonstrated enhanced anticancer efficacy, revolutionizing the traditional perspective on cancer treatment and marking significant advancements in targeted anticancer therapeutics. Currently, over 90 types of PDCs are undergoing clinical trials globally, with representative examples outlined in Table S3. However, PDCs still face certain challenges, such as the susceptibility of peptide-based drugs to enzymatic hydrolysis *in vivo*, which diminishes their bioavailability and therapeutic efficacy [52]. Peptide-based drugs often exhibit a short half-life, necessitating frequent administration and increasing the burden on patients. Furthermore, the challenge of further enhancing targeting specificity to minimize side effects persists. Consequently, the primary research focuses on PDCs include the exploration of novel peptide sequences to improve targeting and stability, the design of multifunctional peptides that simultaneously target multiple receptors to enhance therapeutic efficacy, and the improvement of PDC stability and bioavailability [54]. For instance, Zhou et al. developed the cyclic peptide Cyclo-GCGPep1, which exhibited a high affinity for HER2 based on computational simulations of antibody binding to the HER2 protein. They constructed PDCs with camptothecin (CPT), preserving CPT's pro-apoptotic and Topo I inhibitory properties while demonstrating effective targeting of HER2-positive cells [55]. As research progresses, PDCs are anticipated to become increasingly targeted, biocompatible, and safe, making significant contributions to cancer therapy and human health.

3.3.2. Peptide-drug co-assembling

PDCs have demonstrated significant potential in enhancing

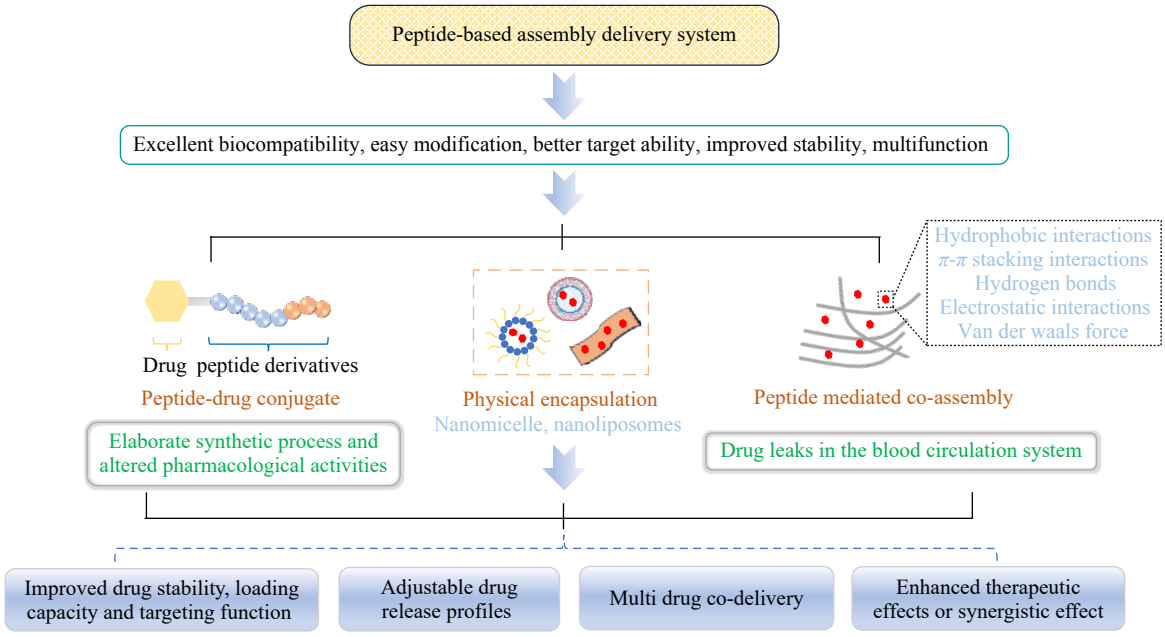

Fig. 3 Illustration of the peptide-based delivery system.

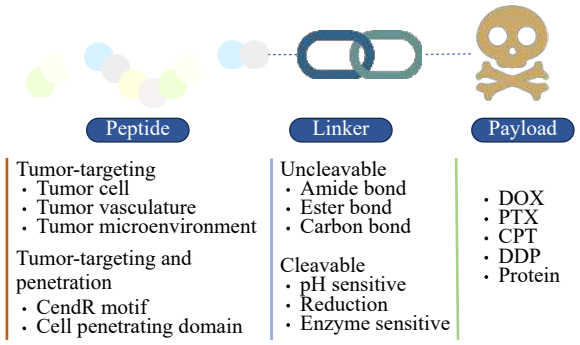

Fig. 4 The structure of PDCs.

drug targeting and efficacy; however, their stability and bioavailability remain challenging. Furthermore, the use of covalent conjugation is complicated by intricate synthesis processes and potential alterations to pharmacological activity. To address these limitations, nanomaterial delivery systems have emerged as an innovative solution, attracting increasing attention. The advancement of nanomedicine has led to substantial progress in nanodrug delivery systems, including nanotubes, nanofibers, micelles, and nanoparticles [56-58]. These systems have been shown to enhance the therapeutic effects of anticancer drugs, reduce side effects, and improve drug solubility [47, 59-69]. Nevertheless, challenges persist, such as the lack of optimal biocompatibility when utilizing inorganic materials and the potential to elicit immune responses. Moreover, the complexity of synthetic polymer structures limits their application, resulting in suboptimal delivery outcomes [70-74]. Consequently, there is a pressing need to develop non-toxic, highly efficient delivery systems with superior targeting capabilities. In this context, peptide self-assembly has emerged as a promising new class of nanomaterials. Peptide self-assembly involves non-covalent interactions that facilitate the spontaneous formation of well-ordered architectures [49, 75, 76]. Depending on their distinct physical properties, these peptides can form various nanostructures, including nanoparticles, nanotubes, nanofibers, micelles, supramolecular hydrogels, and dendrimers [77-83]. Currently, peptide-based self-assembly is widely investigated for drug delivery applications (Fig. 5).

Researchers are diligently working to develop innovative cancer drug delivery systems utilizing self-assembling peptide materials composed of short peptides. These systems can incorporate single amino acids, dipeptides, or tripeptides [84, 85]. Extensive research has also been conducted on larger peptide self-assemblies and hybrid assemblies for cancer drug delivery systems. Certain peptides possess specific biological activities, such as antibacterial, anticancer, and cell growth-promoting functions, and their activity and stability are enhanced through self-assembly [76, 86-93]. Moreover, external stimulus-responsive self-assembly is a crucial nanotechnology employed in the design and construction of functional nanostructures that respond to external stimuli [94-96]. These self-assembled systems can achieve structural reorganization, drug release, or signal transmission in response to changes in external conditions such as light, temperature, pH value, or the presence of biomolecules [66, 97-103]. For instance, Zhu et al. designed a pH-responsive nonapeptide hydrogel fabricated for the delivery of the tumor-targeting drug doxorubicin (DOX). They synthesized a nonapeptide named P1 using the solid-phase synthesis method, which structurally resembles a surfactant-like peptide (SLP) due to its hydrophobic tail and hydrophilic head. *In vitro* drug release studies demonstrated that the DOX-P1 hydrogel was highly sensitive to acidic conditions. Furthermore, *in vivo* experiments showed that the DOX-P1 hydrogel could amplify the therapeutic effect and increase DOX accumulation at the tumor site [104]. Liu et al. developed an injectable pH-responsive OE peptide hydrogel for delivering the anticancer drugs Pentatonix

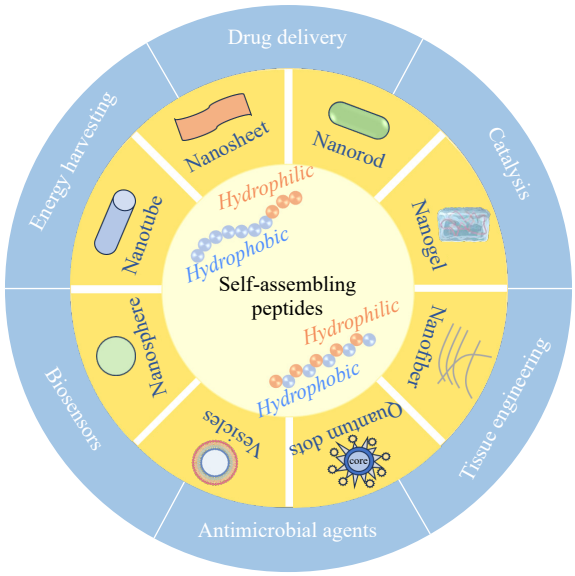

Fig. 5 Application fields of peptide self-assembled nanostructures.

(PTX) and Gemcitabine (GEM). These drugs can be simultaneously released at the tumor site to achieve anticancer effects [105]. As research on self-assembled peptide materials progresses, it is anticipated that more cancer drug delivery systems with robust targeting, excellent biocompatibility, and high safety will be developed. These systems are expected to gain wider clinical application, leading to new breakthroughs in cancer treatment. Future research directions may include more complex self-assembled structures, more efficient external stimulus-response mechanisms, and the integration of other nanotechnologies to further enhance the precision and efficacy of drug delivery.

In conclusion, peptides exhibit significant promise in cancer therapy. Researchers have employed diverse approaches, including ACPs, immunotherapy, novel PDCs, and self-assembled nanotechnology, to enhance drug specificity, efficacy, and safety. Future research will focus on optimizing peptide structure design and improving delivery systems to further refine the clinical application of peptide-based cancer treatments.

4. Peptides in type 2 diabetes mellitus (T2DM) and obesity

In China, T2DM represents the most prevalent form of diabetes, encompassing over 90% of adult diabetic patients [106]. Obesity constitutes a significant risk factor for T2DM, as excess body weight contributes to insulin resistance, resulting in inadequate blood sugar control [107]. Furthermore, obesity can precipitate chronic inflammation and metabolic dysfunction, exacerbating the progression and manifestation of T2DM [108]. Recent advancements highlight the promising potential of peptide-based therapeutics in the management of T2DM and obesity, including GLP-1 receptor agonists, melanocortin-4 receptor agonists, and amylin receptor agonists [109-111]. Notably, GLP-1 receptor agonists predominate the research landscape, accounting for more than 90% of investigations. Consequently, this section provides a comprehensive overview of GLP-1 receptor agonists.

4.1. Structure and action mechanism

GLP-1, a 30-amino acid peptide, is released from gut enteroendocrine cells in response to the stimulation of luminal nutrients immediately following meal ingestion. The bioactive forms secreted from gut enteroendocrine L cells are *N*-terminally truncated GLP-1(7-37) and GLP-1(7-36)NH_2 [112]. In a hyperglycemic state, GLP-1 stimulates insulin secretion by binding to GLP-1 re-

ceptors on pancreatic beta cells, contributing to the reduction of blood sugar levels. Additionally, it inhibits glucagon secretion by pancreatic alpha cells, further diminishing hepatic glucose output and lowering blood sugar levels. Moreover, GLP-1 can decelerate gastric emptying and prolong the residence time of food in the stomach, thereby delaying glucose absorption and aiding in the regulation of postprandial blood sugar. GLP-1 also acts on the central nervous system, particularly the hypothalamus, increasing satiety and reducing food intake, which assists in weight management [113]. However, the rapid degradation by dipeptidyl peptidase-4 (DPP-IV) and kidney filtration limits the half-life of endogenous GLP-1, rendering it unsuitable for use as a therapeutic agent [114]. Consequently, the primary objective of the early development of GLP-1-based medications was to extend the half-life of GLP-1.

4.2. Marketed drugs and clinical research

Several long-acting GLP-1 receptor agonists are available, including dulaglutide, liraglutide, and semaglutide [113]. These agonists are primarily utilized in the treatment of T2DM. Recent clinical trials have revealed that they also provide significant weight loss benefits [115, 116]. Semaglutide, liraglutide, and tirzepatide have received approval for weight loss purposes (Table S4).

Oral semaglutide, developed by Novo Nordisk, has demonstrated promising results in clinical trials for weight loss and has received FDA approval for market release. However, with a bioavailability of less than 1%, there is significant potential for further development [117, 118]. Additionally, to enhance the weight loss effects of GLP-1 drugs and minimize adverse reactions, the development of multi-target drugs has emerged as another avenue for advancement. GIP, glucagon, and amylin receptors have become popular targets for synergistic action with GLP-1 receptors [119, 120]. Beyond the already approved tirzepatide (GLP-1/GIP receptor), leading developments in multi-target formulations include mazdutide (GLP-1/glucagon receptor) by Zeinda Bio, retatrutide (GLP-1/GIP/glucagon receptor) by Eli Lilly, and CagriSema (a combination formulation of GLP-1 receptor agonist and amylin receptor agonist) by Novo Nordisk [121-124].

4.3. Modification strategies

Prior research on GLP-1 has primarily concentrated on its long-acting effects. Common methods for extending the duration of action of GLP-1 include PEG modification and fatty acid acidification [125-128]. For instance, Han et al. synthesized Xenopus GLP-1 and xGLP-1B analogs, conjugating PEG chains of varying molecular weights to the peptides, resulting in a series of PEGylated conjugates [129, 130]. Furthermore, Han et al. designed and synthesized a series of GLP-1 fatty chain conjugates and coumarin-modified GLP-1 derivatives [131-133]. All conjugates maintained significant GLP-1 receptor activation potency while exhibiting enhanced albumin-binding properties and *in vitro* plasma stability. Sustained-release microspheres represent another frequently employed long-term method. For example, Zhang et al. chemically cross-linked two pH-responsive biomaterials, alginate, and hyaluronic acid, to create a novel material for encapsulating exenatide in microspheres. The bioavailability of the exenatide-loaded microspheres, compared to subcutaneous exenatide injection, reached 10.2% [134]. Ruan et al. synthesized and evaluated a novel GLP-1 analog (PGLP-1) with an extended half-life. Subsequently, they prepared PGLP-1-loaded poly (d, l-lactide-co-glycolide) microspheres to achieve long-term effects on blood glucose control [135].

Current research on GLP-1 primarily centers on oral GLP-1 receptor agonist formulations and GLP-1-based multi-target drugs. The development of oral formulations must surmount the obstacles posed by the acidic environment and proteolytic degradation in the gastrointestinal tract. To enhance peptide bioavailability, researchers have employed various strategies, including the optimization of drug delivery systems and the refinement of formulations, such as liposomes, microspheres, and nanocarriers [136, 137]. GLP-1-based multi-target drugs have demonstrated remarkable efficacy in clinical settings, and ongoing research endeavors to combine GLP-1 with targets beyond the gastrointestinal tract to achieve superior therapeutic outcomes [120, 137, 138].

The development of long-acting GLP-1 receptor agonists, oral GLP-1 receptor agonists, and GLP-1-based multi-target drugs represents significant innovative trajectories in the treatment of diabetes and obesity. As research progresses, future investigations may focus on ultra-long-acting GLP-1 receptor agonists, while oral administration will optimize drug formulations and delivery systems to enhance efficacy and safety. Furthermore, combining GLP-1 with other targets has the potential to mitigate the side effects associated with GLP-1, such as weight rebound and muscle mass reduction. These novel treatment approaches will offer patients more efficient, convenient, and comprehensive therapeutic strategies.

5. Peptides in antimicrobial applications

Antibiotics, one of the most significant medical advances of the 20th century, have saved millions of lives worldwide [139]. However, the misuse of antibiotics has led to antimicrobial resistance, limiting treatment options for bacterial infections, especially those caused by multidrug-resistant bacteria. This situation necessitates the development of novel or alternative antibacterial drugs [140]. Antimicrobial peptides (AMPs) have gained prominence as potential alternatives to traditional antibiotics. As crucial components of the innate immune system, AMPs exhibit a broad-spectrum antimicrobial activity against bacteria, fungi, viruses, and parasites [141]. Due to their extensive antimicrobial activity and lower potential for resistance development, these peptide molecules are now considered frontline defenses against multidrug-resistant microbial infections [142].

5.1. Structure and action mechanism

Over 3000 naturally occurring or synthetically produced AMPs have been discovered and documented. AMPs can be categorized into four primary types based on their structural properties: α-helical, β-sheet, cyclic, and those abundant in particular amino acids [143]. This classification system highlights the structural heterogeneity of AMPs and implies that different categories of AMPs may function through unique mechanisms of action.

The antimicrobial mechanisms of AMPs primarily involve disrupting microbial cell membranes, interfering with vital intracellular processes, and modulating the host's immune response to enhance infection resistance. AMPs act by directly interacting with bacterial membranes to create pores, resulting in the loss of cellular contents and thus rapidly killing or inhibiting the microbes. Furthermore, some AMPs can penetrate cell membranes, directly disrupt bacterial metabolic pathways, or block crucial intracellular signaling pathways. In addition to their direct antimicrobial effects, AMPs can also modulate host immune cells to enhance the body's overall resistance to infections [144, 145].

The unique characteristics of AMPs highlight their potential as pioneering agents in the forthcoming era of anti-infection therapies, particularly in light of the escalating global crisis of antibiotic resistance. AMPs present a promising and potent approach to tackle this pressing issue, emphasizing their substantial application prospects within the domain of infection control and treatment.

5.2. Marketed drugs and clinical research

The market features several AMPs, such as colistin, daptomycin, and polymyxin B. These drugs primarily target the treatment of infections caused by recalcitrant Gram-negative bacteria and have demonstrated effective therapeutic outcomes. For instance, colistin, an older drug repurposed as a peptide antibiotic, is employed in treating severe infections caused by multidrug-resistant Gram-negative bacteria. Furthermore, daptomycin, a lipopeptide antibiotic, is utilized for the treatment of serious skin and soft tissue infections by disrupting the integrity of bacterial cell membranes, resulting in cell death [146-148].

In the realm of clinical research, numerous AMPs are undergoing trials to investigate their potential applications in the treatment of infections. MBI-226, a peptide drug currently in phase III clinical trials, aims to address catheter-related bloodstream infections. This drug has exhibited activity against Candida in animal models, providing a scientific foundation for its clinical utilization. Moreover, indolicidin analogs are being evaluated in phase II and III clinical trials for their efficacy in treating acute acne and combating methicillin-resistant Staphylococcus aureus (MRSA). These studies not only demonstrate the capabilities of AMPs in addressing common bacterial infections but also highlight their significant potential against drug-resistant strains [149].

5.3. Modification strategies

Current research on AMPs focuses on several key areas to address the limitations of existing peptides and expand their market applications: 1) Structure-function relationship studies: this research aims to elucidate the antimicrobial mechanisms of peptides by analyzing their amino acid sequences, three-dimensional (3D) structures, and interactions with bacterial cell membranes. These studies guide the design and modification of new AMPs to enhance their efficacy [150]. 2) Synthesis and modification research: researchers employ chemical synthesis and genetic engineering techniques to synthesize and modify AMPs, seeking to improve their stability, antimicrobial activity, and selectivity while reducing toxicity and cost. Methods include amino acid substitution, cyclization, and the integration of other functional sequences [151]. 3) Resistance studies: this research explores the mechanisms by which bacteria develop resistance to AMPs, aiming to find ways to mitigate resistance. These studies typically analyze changes in bacterial gene expression, mutation rates, and adaptive responses under the pressure of AMPs, ensuring long-term effectiveness in clinical applications [152]. 4) Multifunctional AMP research: researchers are investigating peptides that possess multiple functional activities, such as antimicrobial, antiviral, anti-inflammatory, and immunomodulatory properties, to broaden their application scope. These multifunctional AMPs operate through various mechanisms, including directly killing pathogens, modulating immune responses, and reducing inflammation (Table S5).

In summary, AMPs are broad-spectrum antibiotics that exert their effects by disrupting cell membranes or targeting intracellular metabolic processes. They offer several advantages, including a rapid onset of antimicrobial activity, low susceptibility to drug resistance, and multifunctional biological activity, positioning them as a focus in biomedical research. Future research will focus on further optimizing the stability and biological activity of AMPs and explore their full clinical potential. Additionally, exploration will be conducted to address the challenges of drug resistance and to meet the multifunctional clinical needs associated with AMPs.

6. Peptides in neurodegenerative diseases

Neurological diseases impact the central nervous system, which encompasses the brain and spinal cord, or the peripheral nervous system, consisting of nerves and ganglia in other regions of the body. Prevalent neurological disorders include Alzheimer's disease (AD) [153], Parkinson's disease (PD) [154], multiple sclerosis [155], and epilepsy [156]. AD and PD, as globally widespread neurodegenerative diseases, have garnered significant attention from the scientific community. The common characteristic of these diseases is the misfolding of proteins and the formation of amyloid fibrils, which contribute to neuronal dysfunction and cell death. Peptides present promising avenues for treating illnesses associated with protein misfolding and aggregation due to their low toxicity, high target affinity, favorable membrane permeability, effective blood-brain barrier penetration, and low immunogenicity [157].

6.1. Structure and action mechanism

Peptide-based drugs inhibit the aggregation of misfolded proteins by mimicking or blocking interactions with key proteins associated with disease. For example, certain peptides can directly interact with beta-amyloid (Aβ), preventing its aggregation or facilitating its degradation [158]. These peptides are typically designed with high specificity to precisely target critical proteins involved in the pathological process, such as Aβ, tau protein, or alpha-synuclein. Thus, for the prevention and treatment of neurodegenerative diseases, it is essential to investigate the molecular mechanisms underlying protein misfolding and amyloid fibril formation, identify the sources of cytotoxicity and pathological states induced by amyloid fibrils, and develop effective therapeutics to inhibit protein misfolding and aggregation [159].

The potential of peptide-based therapy methods renders them highly relevant in the quest for innovative treatments targeting neurodegenerative disorders. By specifically addressing the pathogenic processes that drive disease progression, these approaches may constitute a significant improvement over traditional treatment options.

6.2. Modification strategies

Current research on peptide-based drugs for neurodegenerative diseases primarily remains at the *in vitro* and cellular experimental levels, with few peptides progressing to preclinical studies and none yet demonstrating efficacy in clinical settings. Researchers are actively investigating these mechanisms and developing peptide-based drugs to further explore the pathogenic mechanisms of degenerative diseases [160]. For instance, Shen et al. demonstrated that *in vivo* overexpression of Dishevelled-2 (DVL-2), mimicking von Hippel-Lindau (VHL) inactivation, conferred protection against Parkinson's disease (PD). Subsequently, they designed a competing peptide, Tat-DDF-2, to inhibit the interaction between VHL and DVL-2, which exhibited pharmacological potential for PD protection *in vitro* and *in vivo* [160]. Yao et al. assessed several peptides containing Gly-Ser-Ala (SNP) sequences that tend to form *β*-sheets. They discovered that SNP-9 is an effective neuroprotective peptide that reduces Aβ oligomers by co-assembling with toxic Aβ oligomers to form hetero-oligomers, demonstrating potential as an Alzheimer's disease treatment [161]. Liu et al. evaluated the neuroprotective effect of walnut peptide (WP) against oxidative stress on PC12 cells, finding that WP suppressed H_2O_2-induced cell death in PC12 cells. In the zebrafish model, WP exhibited a notable neuroprotective effect [162]. Zhang et al. designed and synthesized an apolipoprotein E mimetic peptide (MOP) that can reduce Aβ deposition by inhibiting Aβ aggregation and accelerating Aβ clearance. MOP can self-assemble into various nanostructures, enhancing blood-brain barrier (BBB) permeability [163]. Guo et al. designed a fusion peptide TPL containing BBB-penetrating peptide TGN and neuron-binding

peptide Tet1 connected *via* a tetraglycine linker. Compared to Tet1 or CGN alone, the fusion peptide TPL exhibits improved blood stability and enhanced structural flexibility, resulting in higher binding affinity with GT1b ganglioside receptors or brain capillary endothelial bEnd.3 cells. Administration of TPL-NP in AD mice significantly improved cognitive performance, downregulated tau phosphorylation levels, promoted axonal transport, and attenuated microgliosis, markedly enhancing AD treatment efficacy [164].

Future research may demonstrate that treating degenerative diseases with a multifaceted therapeutic approach, such as disrupting the amyloid fibrillation process, can yield highly successful outcomes. Moreover, the development of biomarkers based on the amyloid fibrillation process is essential for the identification and diagnosis of disorders, the evaluation of treatment efficacy, and the early detection of degenerative diseases. This approach has the potential to significantly improve outcomes by providing treatment options and enhancing our ability to identify and monitor these diseases in their early stages.

7. Summary and outlook

Due to their distinct properties, peptides have been extensively employed in the treatment of cancer, diabetes, obesity, bacterial infections, and nervous system disorders. Furthermore, peptides have demonstrated significant potential in addressing rare diseases, autoimmune conditions, cardiovascular ailments, and immune system disorders. In comparison with small molecule drugs, peptide-based drugs exhibit high specificity and low toxicity, enabling targeted interactions with specific receptors or molecules, thereby reducing adverse effects and minimizing the risk of drug resistance. This approach not only deviates from the conventional treatment paradigm of small molecule drugs but also serves as a valuable complement to existing therapeutic strategies. However, peptide-based drugs face challenges such as low oral bioavailability, susceptibility to degradation by digestive enzymes, poor stability, high preparation and production costs, and complex synthesis and modification processes. These characteristics endow peptide medicines with immense potential while simultaneously presenting numerous obstacles in research and application. Therefore, we propose that the following considerations should be taken into account when investigating peptide-based drugs.

The rapid degradation of peptide-based drugs by enzymes and their limited bioavailability present significant challenges to their clinical application. To mitigate this issue, the incorporation of non-natural amino acids has emerged as a widely employed modification strategy. These modifications can enhance the stability, biological activity, pharmacokinetic properties, and targeting capabilities of peptides. Common non-natural amino acid modifications include substituting L-amino acids with D-amino acids, inserting *N*-alkylated amino acids, and incorporating β-amino acids, α-substituted α-amino acids, or β-substituted α-amino acids [165, 166]. The use of D-amino acids involves replacing metabolically labile natural L-amino acids, which are highly susceptible to proteolytic degradation, with their 3D mirror images [167, 168]. The *N*-alkyl group influences the conformational flexibility of the peptide backbone and nearby residue side chains, eliminates the dominance of the *trans vs cis* peptide bond configuration, and affects certain intra- and intermolecular hydrogen bonds. Furthermore, the adjacent carbonyl group contributes to increased basicity and reduced polarity [169]. Replacing α-amino acids with β-amino acids enhances the biological activity and proteolytic stability of peptides, with the strategic insertion of a single β-amino acid being sufficient to confer proteolytic stability [170]. α-Substituted α-amino acids can introduce conformational constraints into the peptide backbone, thereby increasing peptide resistance to proteolytic degradation [171]. β-Substituted α-amino acids are frequently utilized to induce specific conformational changes in the side chains, typically resulting in increased biological activity and stability of the modified peptides [172]. In conclusion, the introduction of non-natural amino acid modifications significantly improves the performance of peptide-based drugs, highlighting their enhanced potential in the treatment of complex diseases.

A critical consideration is the potential immunogenicity of peptide therapeutics, which may lead to inefficacy or severe adverse reactions. Future studies should focus on optimizing peptide structure and sequence to minimize immunogenicity. Strategies such as humanization, peptide sequence optimization, and surface modifications can contribute to reducing the immunogenicity of peptide-based medications. Furthermore, immunomodulatory technology-based drug delivery systems, including immunoblotting nanoparticles and immunomodulatory peptides, offer promising avenues for mitigating the immunogenic potential of peptide-based drugs [173-177].

Peptides represent a highly valuable therapeutic agent, and the potential for oral administration carries significant implications for enhancing patient compliance and convenience. Oral semaglutide and octreotide exemplify the successful combination of peptide characteristics with permeability enhancers, despite their bioavailability being less than 1%. While challenges such as gastrointestinal enzymatic degradation, limited absorption rates, and instability persist, researchers have made steady progress in overcoming these obstacles through the utilization of chemical modifications, nanoparticle carriers, and enzyme inhibitors [140]. We posit that future peptide-based research should prioritize the improvement of stability and bioavailability while concurrently reducing immunogenicity. Moreover, oral peptides represent a burgeoning area of research, diverging from the traditional peptide-based therapy paradigm. Through sustained innovation and optimization, peptide-based pharmaceuticals hold the potential to significantly expand their market presence and contribute substantially to the advancement of medical science.

In conclusion, peptide-based drugs hold immense potential for the treatment of a wide array of medical conditions. While peptide drugs face numerous challenges in clinical applications, such as delivery efficiency, stability, and immunogenicity, ongoing technological advancements and research endeavors suggest that peptides are poised to become a crucial tool in addressing a broad spectrum of diseases. Future research should prioritize enhancing the stability and bioavailability of peptide-based drugs, mitigating their immunogenicity, developing oral peptide formulations, and exploring novel applications. Through continuous innovation and optimization, peptide pharmaceuticals are expected to offer novel therapeutic options for patients, ultimately improving their quality of life and making significant contributions to medical progress.

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 82173674 and 82204195).

Declaration of competing interest

These authors have no conflict of interest to declare.

References

1 Lau JL, Dunn MK. Therapeutic peptides: historical perspectives, current development trends, and future directions. *Bioorg Med Chem*. 2018;26(10): 2700-2707. https://doi.org/10.1016/j.bmc.2017.06.052.
2 Muttenthaler M, King GF, Adams DJ, et al. Trends in peptide drug discovery. *Nat Rev Drug Discov*. 2021;20(4):309-325. https://doi.org/10.1038/s41573-020-00135-8.
3 Research GV. Peptide therapeutics market size, share & trends analysis

report by application, by type of manufacturers, by route of administration, by synthesis technology, by region, and segment forecasts, 2024–2030. Report No. 978-1-68038-179-5. Grand View Research, San Francisco, 2022: 110
4 Novo Nordisk's blockbuster Ozempic boasts 23% sales surge in 2023. https://www.pharmaceutical-technology.com/analyst-comment/novo-nordisk-ozempic/.
5 Tirzepatide, introduced by Eli Lilly in May 2022, recorded sales of USD 2. 958 billion over the same period. https://www.fiercepharma.com/pharma/q1-lilly-takes-over-top-spot-novo-and-could-stay-there-while.
6 Sharma K, Sharma KK, Sharma A, et al. Peptide-based drug discovery: current status and recent advances. *Drug Discov Today*. 2023;28(2):103464. https://doi.org/10.1016/j.drudis.2022.103464.
7 Strohl WR. Fusion proteins for half-life extension of biologics as a strategy to make biobetters. *Biodrugs*. 2015;29(4):215-239. https://doi.org/10.1007/s40259-015-0133-6.
8 Kurtzhals P, Ostergaard S, Nishimura E, et al. Derivatization with fatty acids in peptide and protein drug discovery. *Nat Rev Drug Discov*. 2023;22(1):59-80. https://doi.org/10.1038/s41573-022-00529-w.
9 Lee MF, Poh CL. Strategies to improve the physicochemical properties of peptide-based drugs. *Pharm Res*. 2023;40(3):617-632. https://doi.org/10.1007/s11095-023-03486-0.
10 Liu X, Liu X, Sunchen S, et al. A novel tumor-activated ALA fusion protein for specific inhibition on the growth and invasion of breast cancer cells MDA-MB-231. *Drug Deliv*. 2017;24(1):1811-1817. https://doi.org/10.1080/10717544.2017.1406560.
11 Shen X, Li Q, Wang F, et al. Generation of a novel long-acting thymosin alpha1-Fc fusion protein and its efficacy for the inhibition of breast cancer *in vivo*. *Biomed Pharmacother*. 2018;108:610-617. https://doi.org/10.1016/j.biopha.2018.09.064.
12 Wang F, Li B, Fu P, et al. Immunomodulatory and enhanced antitumor activity of a modified thymosin alpha1 in melanoma and lung cancer. *Int J Pharm*. 2018;547(1-2):611-620. https://doi.org/10.1016/j.ijpharm.2018.06.041.
13 Shen X, Wang L, Xu C, et al. Fusion of thymosin alpha 1 with mutant IgG1 CH3 prolongs half-life and enhances antitumor effects *in vivo*. *Int Immunopharmacol*. 2019;74:105662. https://doi.org/10.1016/j.intimp.2019.05.047.
14 Li C, Zhao N, An L, et al. Apoptosis-inducing activity of synthetic hydrocarbon-stapled peptides in H358 cancer cells expressing KRAS(G12C). *Acta Pharm Sin B*. 2021;11(9):2670-2684. https://doi.org/10.1016/j.apsb.2021.06.013.
15 Chen J, Bian J, Hantash BM, et al. Enhanced skin retention and permeation of a novel peptide *via* structural modification, chemical enhancement, and microneedles. *Int J Pharm*. 2021;606:120868. https://doi.org/10.1016/j.ijpharm.2021.120868.
16 Yao J, Fan Y, Li Y, et al. Strategies on the nuclear-targeted delivery of genes. *J Drug Target*. 2013;21(10):926-939. https://doi.org/10.3109/1061186X.2013.830310.
17 Xu M, Chen Y, Banerjee P, et al. Dendritic cells targeting and pH-responsive multi-layered nanocomplexes for smart delivery of DNA vaccines. *AAPS PharmSciTech*. 2017;18:2618-2625. https://doi.org/10.1208/s12249-017-0741-1.
18 Wang YT, Huang LP, Shen Y, et al. Electrostatic interactions between polyglutamic acid and polylysine yields stable polyion complex micelles for deoxypodophyllotoxin delivery. *Int J Nanomed*. 2017;12:7963-7977. https://doi.org/10.2147/IJN.S140573.
19 Xu Y, Lu S, Liu Q, et al. Preparation, intestinal segment stability, and mucoadhesion properties of novel thymopentin-loaded chitosan derivatives coated with poly (*n*-butyl) cyanoacrylate nanoparticles. *Int J Nanomedicine*. 2019;14:1659-1668. https://doi.org/10.2147/IJN.S194529.
20 Merrifield RB. Solid-phase peptide synthesis. *Adv Enzymol Relat Areas Mol Biol*. 1969;32:221-296. https://doi.org/10.1002/9780470122778.ch6.
21 Agouridas V, Diemer V, Melnyk O. Strategies and open questions in solid-phase protein chemical synthesis. *Curr Opin Chem Biol*. 2020;58:1-9. https://doi.org/10.1016/j.cbpa.2020.02.007.
22 Sharma A, Kumar A, De La Torre BG, et al. Liquid-phase peptide synthesis (LPPS): a third wave for the preparation of peptides. *Chem Rev*. 2022;122(16):13516-13546. https://doi.org/10.1021/acs.chemrev.2c00132.
23 Ahn CB, Cho YS, Je JY. Purification and anti-inflammatory action of tripeptide from salmon pectoral fin byproduct protein hydrolysate. *Food Chem*. 2015;168:151-156. https://doi.org/10.1016/j.foodchem.2014.05.112.
24 Chalamaiah M, Hemalatha R, Jyothirmayi T, et al. Immunomodulatory effects of protein hydrolysates rohu (*Labeo rohita*) egg (roe) in BALB/c mice. *Food Res Int*. 2014;62:1054-1061. https://doi.org/10.1016/j.foodres.2014.05.050.
25 Moreno-Montoro M, Jauregi P, Navarro-Alarcón M, et al. Bioaccessible peptides released by *in vitro* gastrointestinal digestion of fermented goat milks. *Anal Bioanal Chem*. 2018;410(15):3597-3606. https://doi.org/10.1007/s00216-018-0983-0.
26 Piers KL, Brown MH, Hancock REW. Recombinant-DNA procedures for producing small antimicrobial cationic peptides in bacteria. *Gene*. 1993;134(1):7-13. https://doi.org/10.1016/0378-1119(93)90168-3.
27 Herbel V, Schäfer H, Wink M. Recombinant production of snakin-2 (an antimicrobial peptide from tomato) in and analysis of its bioactivity. *Molecules*. 2015;20(8):14889-14901. https://doi.org/10.3390/molecules200814889.
28 Qiao X, Wang Y, Yu H. Progress in the mechanisms of anticancer peptides. *Chin J Biotechnol*. 2019;35(8):1391-1400. https://doi.org/10.13345/j.cjb.190033.
29 Hilchie AL, Hoskin DW, Power Coombs MR. Anticancer activities of natural and synthetic peptides. *Adv Exp Med Biol*. 2019;1117:131-147. https://doi.org/10.1007/978-981-13-3588-4_9.
30 Chiangjong W, Chutipongtanate S, Hongeng S. Anticancer peptide: physicochemical property, functional aspect and trend in clinical application (Review). *Int J Oncol*. 2020;57(3):678-696. https://doi.org/10.3892/ijo.2020.5099.
31 Pan X, Xu J, Jia X. Research progress evaluating the function and mechanism of anti-tumor peptides. *Cancer Manag Res*. 2020; 12:397-409. https://doi.org/10.2147/CMAR.S232708.
32 Hu J, Yan M, Pu C, et al. Chemically synthesized matrix metalloproteinase and angiogenesis-inhibiting peptides as anticancer agents. *Anticancer Agents Med Chem*. 2014;14(3):483-494. https://doi.org/10.2174/1871520614031402071656 32.
33 Wang F, Zhang R, Li B, et al. A cell-internalizing peptide endows tumstatin7 with enhanced antitumor properties. *Pharmazie*. 2018;73(12):715-720. https://doi.org/10.1691/ph.2018.8623.
34 Li HM, Dong ZP, Wang QY, et al. *De novo* computational design for development of a peptide ligand oriented to VEGFR-3 with high affinity and long circulation. *Mol Pharm*. 2017;14(7):2236-2244. https://doi.org/10.1021/acs.molpharmaceut.7b00070.
35 Setrerrahmane S, Yu J, Hao J, et al. Novel production method of innovative antiangiogenic and antitumor small peptides in *Escherichia coli*. *Drug Des Devel Ther*. 2017;11:3207-3220. https://doi.org/10.2147/DDDT.S136957.
36 Li M, Xu H, Wang J. Optimized functional and structural design of dual-target LMRAP, a bifunctional fusion protein with a 25-amino-acid antitumor peptide and GnRH Fc fragment. *Acta Pharm Sin B*. 2020;10(2):262-275. https://doi.org/10.1016/j.apsb.2019.10.010.
37 Kirkwood JM, Butterfield LH, Tarhini AA, et al. Immunotherapy of cancer in 2012. *CA Cancer J Clin*. 2012;62(5):309-335. https://doi.org/10.3322/caac.20132.
38 Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86-104. https://doi.org/10.3322/caac.21596.
39 Carlisle JW, Steuer CE, Owonikoko TK, et al. An update on the immune landscape in lung and head and neck cancers. *CA Cancer J Clin*. 2020;70(6):505-517. https://doi.org/10.3322/caac.21630.
40 Miao Q, Zhang W, Zhang K, et al. Rational design of a potent macrocyclic peptide inhibitor targeting the PD-1/PD-L1 protein-protein interaction. *RSC Adv*. 2021;11(38):23270-23279. https://doi.org/10.1039/D1RA03118J.
41 Tao H, Cheng L, Liu L, et al. A PD-1 peptide antagonist exhibits potent anti-tumor and immune regulatory activity. *Cancer Lett*. 2020;493:91-101. https://doi.org/10.1016/j.canlet.2020.08.009.
42 Tsiatas M, Mountzios G, Curigliano G. Future perspectives in cancer immunotherapy. *Ann Transl Med*. 2016;4(14):273. https://doi.org/10.21037/atm.2016.07.14.
43 Wei X, Chen F, Xin K, et al. Cancer-testis antigen peptide vaccine for cancer immunotherapy: progress and prospects. *Transl Oncol*. 2019;12(5):733-738. https://doi.org/10.1016/j.tranon.2019.02.008.
44 Wang Q, Dong Z, Lou F, et al. Phenylboronic ester-modified polymeric nanoparticles for promoting TRP2 peptide antigen delivery in cancer immunotherapy. *Drug Deliv*. 2022;29(1):2029-2043. https://doi.org/10.1080/10717544.2022.2086941.
45 Shi W, Qiu Q, Tong Z, et al. Synthetic tumor-specific antigenic peptides with a strong affinity to HLA-A2 elicit anti-breast cancer immune response through activating $CD8^{(+)}$ T cells. *Eur J Med Chem*. 2020;189:112051. https://doi.org/10.1016/j.ejmech.2020.112051.
46 Wang M, Liu J, Xia M, et al. Peptide-drug conjugates: a new paradigm for targeted cancer therapy. *Eur J Med Chem*. 2024;265:116119. https://doi.org/10.1016/j.ejmech.2023.116119.
47 Youn Y S, Bae YH. Perspectives on the past, present, and future of cancer nanomedicine. *Adv Drug Deliv Rev*. 2018;130:3-11. https://doi.org/10.1016/j.addr.2018.05.008.
48 Hossen S, Hossain MK, Basher MK, et al. SmSmart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: a review. *J Adv Res*. 2019;15:1-18. https://doi.org/10.1016/j.jare.2018.06.005.
49 Li T, Lu XM, Zhang MR, et al. Peptide-based nanomaterials: self-assembly, properties and applications. *Bioact Mater*. 2021;11:268-282. https://doi.org/10.1016/j.bioactmat.2021.09.029.
50 Wang Y, Cheetham AG, Angacian G, et al. Peptide-drug conjugates as effective prodrug strategies for targeted delivery. *Adv Drug Deliv Rev*. 2017;110-111:112-126. https://doi.org/10.1016/j.addr.2016.06.015.
51 Li S, Roberts RW. A novel strategy for *in vitro* selection of peptide-drug conjugates. *Chem Biol*. 2003;10(3):233-239. https://doi.org/10.1016/S1074-5521(03)00047-4.
52 Cooper BM, Iegre J, Dh OD, et al. Peptides as a platform for targeted therapeutics for cancer: peptide-drug conjugates (PDCs). *Chem Soc Rev*. 2021;50(3):1480-1494. https://doi.org/10.1039/D0CS00556H.
53 Hoppenz P, Els-Heindl S, Beck-Sickinger AG. Peptide-drug conjugates and their targets in advanced cancer therapies. *Front Chem*. 2020;8:571. https://doi.org/10.3389/fchem.2020.00571.
54 Chen Z, Zhang P, Cheetham AG, et al. Controlled release of free doxorubicin from peptide-drug conjugates by drug loading. *J Control Release*. 2014;191:123-130. https://doi.org/10.1016/j.jconrel.2014.05.051.
55 Zhou J, Zou Y, Cai Y, et al. A designed cyclic peptide based on trastuzumab used to construct peptide-drug conjugates for its HER2-targeting ability. *Bioorg Chem*. 2021;117:105453. https://doi.org/10.1016/j.bioorg.2021.105453.
56 Liu D, Chen Y, Wang Q, et al. Tailored protein-conjugated DNA nanoplatform for synergistic cancer therapy. *J Control Release*. 2022;346:250-259. https://doi.org/10.1016/j.jconrel.2022.04.022.
57 Meng FF, Han N, Yeo Y. Organic nanoparticle systems for spatiotemporal control of multimodal chemotherapy. *Expert Opin Drug Del*. 2017;14(3):427-

446. https://doi.org/10.1080/17425247.2016.1218464.
58 He Y, Su Z, Xue L, et al. Co-delivery of erlotinib and doxorubicin by pH-sensitive charge conversion nanocarrier for synergistic therapy. *J Control Release*. 2016;229:80-92. https://doi.org/10.1016/j.jconrel.2016.03.001.
59 Hu D, Mezghrani O, Zhang L, et al. GE11 peptide modified and reduction-responsive hyaluronic acid-based nanoparticles induced higher efficacy of doxorubicin for breast carcinoma therapy. *Int J Nanomedicine*. 2016;11:5125-5147. https://doi.org/10.2147/IJN.S113469.
60 Peng J, Wang Q, Zhou J, et al. Targeted lipid nanoparticles encapsulating dihydroartemisinin and chloroquine phosphate for suppressing the proliferation and liver metastasis of colorectal cancer. *Front Pharmacol*. 2021;12:720777. https://doi.org/10.3389/fphar.2021.720777.
61 Yao Y, Chen H, Tan N. Cancer-cell-biomimetic nanoparticles systemically eliminate hypoxia tumors by synergistic chemotherapy and checkpoint blockade immunotherapy. *Acta Pharm Sin B*. 2022;12(4):2103-2119. https://doi.org/10.1016/j.apsb.2021.10.010.
62 Zhang W, Han B, Gao C, et al. Integrated platform of oxygen self-enriched nanovesicles: SP94 peptide-directed chemo/sonodynamic therapy for liver cancer. *Eur J Pharm Biopharm*. 2022;179:206-220. https://doi.org/10.1016/j.ejpb.2022.09.012.
63 Li F, Zhao Y, Mao C, et al. RGD-modified albumin nanoconjugates for targeted delivery of a porphyrin photosensitizer. *Mol Pharm*. 2017;14(8):2793-2804. https://doi.org/10.1021/acs.molpharmaceut.7b00321.
64 Deng Y, Jiang Z, Jin Y, et al. Reinforcing vascular normalization therapy with a bi-directional nano-system to achieve therapeutic-friendly tumor microenvironment. *J Control Release*. 2021;340:87-101. https://doi.org/10.1016/j.jconrel.2021.10.016.
65 Liu Y, Lu X, Zhang Z, et al. mPEG-Cholic acid/TPGS mixed micelles for combined delivery of paclitaxel and bufalin to treat hepatocellular carcinoma. *Pharm Dev Technol*. 2022;27(2):215-227. https://doi.org/10.1080/10837450.2022.2037140.
66 Chen Q, Zhou S, Ding Y, et al. A bio-responsive, cargo-catchable gel for postsurgical tumor treatment *via* ICD-based immunotherapy. *J Control Release*. 2022;346:212-225. https://doi.org/10.1016/j.jconrel.2022.04.015.
67 Gu Y, Xu C, Wang Y, et al. Multifunctional nanocomposites based on liposomes and layered double hydroxides conjugated with glycylsarcosine for efficient topical drug delivery to the posterior segment of the eye. *Mol Pharm*. 2019;16(7):2845-2857. https://doi.org/10.1021/acs.molpharmaceut.8b01136.
68 Qin C, He B, Dai W, et al. Inhibition of metastatic tumor growth and metastasis *via* targeting metastatic breast cancer by chlorotoxin-modified liposomes. *Mol Pharm*. 2014;11(10):3233-3241. https://doi.org/10.1021/mp400691z.
69 Wu J, Zhao J, Zhang B, et al. Polyethylene glycol-polylactic acid nanoparticles modified with cysteine-arginine-glutamic acid-lysine-alanine fibrin-homing peptide for glioblastoma therapy by enhanced retention effect. *Int J Nanomedicine*. 2014;9:5261-5271. https://doi.org/10.2147/IJN.S72649.
70 Mohammapdour R, Ghandehari H. Mechanisms of immune response to inorganic nanoparticles and their degradation products. *Adv Drug Deliv Rev*. 2022;180:114022. https://doi.org/10.1016/j.addr.2021.114022.
71 Chambre L, Martin-Moldes Z, Parker RN, et al. Bioengineered elastin- and silk-biomaterials for drug and gene delivery. *Adv Drug Deliv Rev*. 2020;160:186-198. https://doi.org/10.1016/j.addr.2020.10.008.
72 Yu LN, Jin Y, Song MJ, et al. When natural compounds meet nanotechnology: nature-inspired nanomedicines for cancer immunotherapy. *Pharmaceutics*. 2022;14(8):1589. https://doi.org/10.3390/pharmaceutics14081589.
73 Tang L, Li J, Zhao QQ, et al. Advanced and innovative nano-systems for anticancer targeted drug delivery. *Pharmaceutics*. 2021;13(8):1151. https://doi.org/10.3390/pharmaceutics13081151.
74 Xu Y, Yao Y, Wang L, et al. Hyaluronic acid coated liposomes co-delivery of natural cyclic peptide RA-XII and mitochondrial targeted photosensitizer for highly selective precise combined treatment of colon cancer. *Int J Nanomedicine*. 2021;16:4929-4942. https://doi.org/10.2147/IJN.S311577.
75 Qi GB, Gao YJ, Wang L, et al. Self-assembled peptide-based nanomaterials for biomedical imaging and therapy. *Adv Mater*. 2018;30(22):e1703444. https://doi.org/10.1002/adma.201703444.
76 Shu C, Sabi-Mouka EMB, Wang X, et al. Self-assembly hydrogels as multifunctional drug delivery of paclitaxel for synergistic tumour-targeting and biocompatibility *in vitro* and *in vivo*. *J Pharm Pharmacol*. 2017;69(8):967-977. https://doi.org/10.1111/jphp.12732.
77 La MS, Di NC, Onesto V, et al. Self-assembling peptides: from design to biomedical applications. *Int J Mol Sci*. 2021;22(23):12662. https://doi.org/10.3390/ijms222312662.
78 Lee S, Trinh THT, Yoo M, et al. Self-assembling peptides and their application in the treatment of diseases. *Int J Mol Sci*. 2019;20(23):5850. https://doi.org/10.3390/ijms20235850.
79 Jin X, Zhou J, Zhang Z, et al. Doxorubicin combined with betulinic acid or lonidamine in RGD ligand-targeted pH-sensitive micellar system for ovarian cancer treatment. *Int J Pharm*. 2019;571:118751. https://doi.org/10.1016/j.ijpharm.2019.118751.
80 Dong Y, Chen Y, Zhu D, et al. Self-assembly of amphiphilic phospholipid peptide dendrimer-based nanovectors for effective delivery of siRNA therapeutics in prostate cancer therapy. *J Control Release*. 2020;322:416-425. https://doi.org/10.1016/j.jconrel.2020.04.003.
81 Zhu D, Zhang H, Huang Y, et al. A self-assembling amphiphilic peptide dendrimer-based drug delivery system for cancer therapy. *Pharmaceutics*. 2021;13(7):1092. https://doi.org/10.3390/pharmaceutics13071092.
82 Shu C, Li TF, Li D, et al. Anticancer activity and pharmacokinetics of tanshinone IIA derivative supramolecular hydrogels. *J Drug Deliv Sci Tec*. 2018;48:509-515. https://doi.org/10.1016/j.jddst.2018.10.024.
83 Sun LL, Zheng CL, Webster TJ. Self-assembled peptide nanomaterials for biomedical applications: promises and pitfalls. *Int J Nanomed*. 2016;12:73-86. https://doi.org/10.2147/IJN.S117501.
84 Gupta S, Singh I, Sharma AK, et al. Ultrashort peptide self-assembly: front-runners to transport drug and gene cargos. *Front Bioeng Biotechnol*. 2020;8:504. https://doi.org/10.3389/fbioe.2020.00504.
85 Jiang T, Ma Y, Xu X, et al. Enzyme-instructed hybrid nanogel/nanofiber oligopeptide hydrogel for localized protein delivery. *Acta Pharm Sin B*. 2021;11(7):2070-2079. https://doi.org/10.1016/j.apsb.2020.11.010.
86 Sun J, Jiang L, Lin Y, et al. Enhanced anticancer efficacy of paclitaxel through multistage tumor-targeting liposomes modified with RGD and KLA peptides. *Int J Nanomedicine*. 2017;12:1517-1537. https://doi.org/10.2147/IJN.S122859.
87 Wang X, Zhang Q, Lv L, et al. Glioma and microenvironment dual targeted nanocarrier for improved antiglioblastoma efficacy. *Drug Deliv*. 2017;24(1):1401-1409. https://doi.org/10.1080/10717544.2017.1378940.
88 Ni Y, Zhao W, Cheng W, et al. Lipopeptide liposomes-loaded hydrogel for multistage transdermal chemotherapy of melanoma. *J Control Release*. 2022;351:245-254. https://doi.org/10.1016/j.jconrel.2022.09.014.
89 Zhang S, Liu Y, Gan Y, et al. Conjugates of TAT and folate with DOX-loaded chitosan micelles offer effective intracellular delivery ability. *Pharm Dev Technol*. 2019;24(2):253-261. https://doi.org/10.1080/10837450.2018.1469147.
90 Wu C, Wang Z, Wang X, et al. Morphology/interstitial fluid pressure-tunable nanopomegranate designed by alteration of membrane fluidity under tumor enzyme and PEGylation. *Mol Pharm*. 2021;18(5):2039-2052. https://doi.org/10.1021/acs.molpharmaceut.1c00036.
91 Xiao H, Zhang R, Fan X, et al. Super-sensitive bifunctional nanoprobe: self-assembly of peptide-driven nanoparticles demonstrating tumor fluorescence imaging and therapy. *Acta Pharm Sin B*. 2022;12(3):1473-1486. https://doi.org/10.1016/j.apsb.2021.07.020.
92 Kong Y, Sun Q, Zhao Q, et al. Purification and characterization of a novel antiplatelet peptide from *Deinagkistrodon acutus* Venom. *Toxins (Basel)*. 2018;10(8):332. https://doi.org/10.3390/toxins10080332.
93 Xin XF, Zhou Y, Lyu Y, et al. Disease-specific corona mediated co-delivery of MTX and siRNA-TNFα by a polypeptide nanoplatform with antigen-scavenging functions in psoriasis. *J Control Release*. 2023;364:326-342. https://doi.org/10.1016/j.jconrel.2023.10.035.
94 Raza F, Zafar H, Zhu Y, et al. A review on recent advances in stabilizing peptides/proteins upon fabrication in hydrogels from biodegradable polymers. *Pharmaceutics*. 2018;10(1):16. https://doi.org/10.3390/pharmaceutics10010016.
95 Sun C, Shen WC, Tu J, et al. Interaction between cell-penetrating peptides and acid-sensitive anionic oligopeptides as a model for the design of targeted drug carriers. *Mol Pharm*. 2014;11(5):1583-1590. https://doi.org/10.1021/mp400747k.
96 Yang Y, Zhao QF, Peng Z, et al. A GSH/CB dual-controlled self-assembled nanomedicine for high-efficacy doxorubicin-resistant breast cancer therapy. *Front Pharmacol*. 2022;12:811724. https://doi.org/10.3389/fphar.2021.811724.
97 Ouahab A, Cheraga N, Onoja V, et al. Novel pH-sensitive charge-reversal cell penetrating peptide conjugated PEG-PLA micelles for docetaxel delivery: *in vitro* study. *Int J Pharm*. 2014;466(1-2):233-245. https://doi.org/10.1016/j.ijpharm.2014.03.009.
98 Chen X, Zhang Y, Tang C, et al. Co-delivery of paclitaxel and anti-survivin siRNA *via* redox-sensitive oligopeptide liposomes for the synergistic treatment of breast cancer and metastasis. *Int J Pharm*. 2017;529(1-2):102-115. https://doi.org/10.1016/j.ijpharm.2017.06.071.
99 Tang B, Zaro JL, Shen Y, et al. Acid-sensitive hybrid polymeric micelles containing a reversibly activatable cell-penetrating peptide for tumor-specific cytoplasm targeting. *J Control Release*. 2018;279:147-156. https://doi.org/10.1016/j.jconrel.2018.04.016.
100 Wang C, Wang X, Zhong T, et al. The antitumor activity of tumor-homing peptide-modified thermosensitive liposomes containing doxorubicin on MCF-7/ADR: *in vitro* and *in vivo*. *Int J Nanomedicine*. 2015;10:2229-2248. https://doi.org/10.2217/nnm.15.48.
101 Jin Y, Wu Z, Wu C, et al. Size-adaptable and ligand (biotin)-sheddable nanocarriers equipped with avidin scavenging technology for deep tumor penetration and reduced toxicity. *J Control Release*. 2020;320:142-158. https://doi.org/10.1016/j.jconrel.2020.01.040.
102 Liu Y, Ye Z, Yang W, et al. A triple enhanced permeable gold nanoraspberry designed for positive feedback interventional therapy. *J Control Release*. 2022;345:120-137. https://doi.org/10.1016/j.jconrel.2022.03.010.
103 Li TF, Li D, Xu XY, et al. A simple injectable peptide-based hydrogel of tanshinone IIA for antioxidant and anticoagulation. *J Drug Deliv Sci Tec*. 2020;58:101532. https://doi.org/10.1016/j.jddst.2020.101532.
104 Zhu J, Gao R, Wang Z, et al. Sustained and targeted delivery of self-assembled doxorubicin nonapeptides using pH-responsive hydrogels for osteosarcoma chemotherapy. *Pharmaceutics*. 2023;15(2):668. https://doi.org/10.3390/pharmaceutics15020668.
105 Liu YF, Ran YC, Ge Y, et al. pH-Sensitive peptide hydrogels as a combination drug delivery system for cancer treatment. *Pharmaceutics*. 2022;14(3):652. https://doi.org/10.3390/pharmaceutics14030652.
106 Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119.
107 Klein S, Gastaldelli A, Yki-Jarvinen H, et al. Why does obesity cause diabetes? *Cell Metab*. 2022;34(1):11-20. https://doi.org/10.1016/j.cmet.2021.12.012.
108 Rohm TV, Meier DT, Olefsky JM, et al. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022;55(1):31-55. https://doi.org/10.1016/j.immuni.2021.12.013.

109 Wang S, Downing G, Olsen KF, et al. Aqueous remote loading of setmelanotide in poly(lactic-co-glycolic acid) microspheres for long-term obesity treatment. *J Control Release*. 2023;364:589-600. https://doi.org/10.1016/j.jconrel.2023.09.015.

110 Riddle MC, Yuen KC, De Bruin TW, et al. Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes. *Diabetes Obes Metab*. 2015;17(9):904-907. https://doi.org/10.1111/dom.12504.

111 Yabut JM, Drucker DJ. Glucagon-like peptide-1 receptor-based therapeutics for metabolic liver disease. *Endocr Rev*. 2023;44(1):14-32. https://doi.org/10.1210/endrev/bnac018.

112 Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87(4):1409-1439. https://doi.org/10.1152/physrev.00034.2006.

113 Helmstadter J, Keppeler K, Kuster L, et al. Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits-the role of the GLP-1 receptor. *Br J Pharmacol*. 2022;179(4):659-676. https://doi.org/10.1111/bph.15462.

114 Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216. https://doi.org/10.1111/dom.12591.

115 Rosenkilde MM. Advances in incretin-based therapeutics for obesity. *Nat Rev Endocrinol*. 2024;20(2):67-68. https://doi.org/10.1038/s41574-023-00938-w.

116 Liu CX, Zou YX, Qian H. GLP-1R agonists for the treatment of obesity: a patent review (2015-present). *Expert Opin Ther Pat*. 2020;30(10):781-794. https://doi.org/10.1080/13543776.2020.1811851.

117 Inokuchi T, Fukumoto Y, Lee G, et al. Efficacy and tolerability of oral semaglutide in Japanese patients with type 2 diabetes mellitus: analysis report from diabetes specialist clinics. *J Diabetes Investig*, 2024;15(9):1202-1210. https://doi.org/10.1111/jdi.14225.

118 Peng HS, Wang JH, Chen JY, et al. Challenges and opportunities in delivering oral peptides and proteins. *Expert Opin Drug Del*. 2023;20(10):1349-1369. https://doi.org/10.1080/17425247.2023.2237408.

119 Nogueiras R, Nauck MA, Tschop MH. Gut hormone co-agonists for the treatment of obesity: from bench to bedside. *Nat Metab*. 2023;5(6):933-944. https://doi.org/10.1038/s42255-023-00812-z.

120 Muller TD, Bluher M, Tschop MH, et al. Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov*. 2022;21(3):201-223. https://doi.org/10.1038/s41573-021-00337-8.

121 Buckley A, Suliman S, Allum M, et al. Real world use of tirzepatide in the treatment of type 2 diabetes in an Arab population. *Diabetes Obes Metab*. 2024;26(8):3381-3391. https://doi.org/10.1111/dom.15680.

122 Ji L, Gao L, Jiang H, et al. Safety and efficacy of a GLP-1 and glucagon receptor dual agonist mazdutide (IBI362) 9 mg and 10 mg in Chinese adults with overweight or obesity: a randomised, placebo-controlled, multiple-ascending-dose phase 1b trial. *EClinicalMedicine*. 2022;54:101691. https://doi.org/10.1016/j.eclinm.2022.101691.

123 Kaur M, Misra S. A review of an investigational drug retatrutide, a novel triple agonist agent for the treatment of obesity. *Eur J Clin Pharmacol*. 2024;80(5):669-676. https://doi.org/10.1007/s00228-024-03646-0.

124 Apovian CM, Mcdonnell ME. CagriSema and the link between obesity and type 2 diabetes. *Lancet*. 2023;402(10403):671-673. https://doi.org/10.1016/S0140-6736(23)01291-6.

125 Tang D, Tian H, Wu J, et al. *C*-terminal site-specific PEGylated exendin-4 analog: a long-acting glucagon like peptide-1 receptor agonist, on glycemic control and beta cell function in diabetic db/db mice. *J Pharmacol Sci*. 2018;138(1):23-30. https://doi.org/10.1016/j.jphs.2018.08.009.

126 Sun L, Huang X, Han J, et al. Site-specific fatty chain-modified exenatide analogs with balanced glucoregulatory activity and prolonged *in vivo* activity. *Biochem Pharmacol*. 2016;110-111:80-91. https://doi.org/10.1016/j.bcp.2016.04.016.

127 Wu Q, Chen S, Zhu H, et al. Biased agonists with less glucagon-like peptide-1 receptor-mediated endocytosis prolong hypoglycaemic effects. *Eur J Pharmacol*. 2021;907:174203. https://doi.org/10.1016/j.ejphar.2021.174203.

128 Gao MM, Tong Y, Gao XD, et al. Development of a *C*-terminal site-specific PEGylated analog of GLP-1 with improved anti-diabetic effects in diabetic mice. *Drug Develop Res*. 2013;74(3):186-193. https://doi.org/10.1002/ddr.21059.

129 Han J, Chen X, Wang Y, et al. Xenopus GLP-1-inspired discovery of novel GLP-1 receptor agonists as long-acting hypoglycemic and insulinotropic agents with significant therapeutic potential. *Biochem Pharmacol*. 2017;142:155-167. https://doi.org/10.1016/j.bcp.2017.06.132.

130 Han J, Fei Y, Zhou F, et al. Xenopus-derived glucagon-like peptide-1 and polyethylene-glycosylated glucagon-like peptide-1 receptor agonists: long-acting hypoglycaemic and insulinotropic activities with potential therapeutic utilities. *Br J Pharmacol*. 2018;175(3):544-557. https://doi.org/10.1111/bph.14107.

131 Han J, Huang X, Sun L, et al. Novel fatty chain-modified glucagon-like peptide-1 conjugates with enhanced stability and prolonged *in vivo* activity. *Biochem Pharmacol*. 2013;86(2):297-308. https://doi.org/10.1016/j.bcp.2013.05.012.

132 Han J, Sun L, Huang X, et al. Novel coumarin modified GLP-1 derivatives with enhanced plasma stability and prolonged *in vivo* glucose-lowering ability. *Br J Pharmacol*. 2014;171(23):5252-5264. https://doi.org/10.1111/bph.12843.

133 Han J, Sun LD, Qian H, et al. Biological activity studies of the novel glucagon-like peptide-1 derivative HJ07. *Chin J Nat Med*. 2014;12(8):613-618. https://doi.org/10.1016/S1875-5364(14)60093-5.

134 Zhang B, He D, Fan Y, et al. Oral delivery of exenatide *via* microspheres prepared by cross-linking of alginate and hyaluronate. *PLoS One*. 2014;9(1):e86064. https://doi.org/10.1371/journal.pone.0086064.

135 Ruan S, Gu Y, Liu B, et al. Long-acting release microspheres containing novel GLP-1 analog as an antidiabetic system. *Mol Pharm*. 2018;15(7):2857-2869. https://doi.org/10.1021/acs.molpharmaceut.8b00344.

136 Lu W, Tian H, Qian P, et al. An orally available hypoglycaemic peptide taken up by caveolae transcytosis displays improved hypoglycaemic effects and body weight control in db/db mice. *Br J Pharmacol*. 2020;177(15):3473-3488. https://doi.org/10.1111/bph.15069.

137 Aroda VR, Blonde L, Pratley RE. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. *Rev Endocr Metab Disord*. 2022;23(5):979-994. https://doi.org/10.1007/s11154-022-09735-8.

138 Wang LJ. Designing a dual GLP-1R/GIPR agonist from tirzepatide: comparing residues between tirzepatide, GLP-1, and GIP. *Drug Des Dev Ther*. 2022;16:1547-1559. https://doi.org/10.2147/DDDT.S358989.

139 Davies J. Where have all the antibiotics gone? *Can J Infect Dis Med Microbiol*. 2006;17(5):287-290. https://doi.org/10.1155/2006/707296.

140 Shallcross LJ, Davies DS. Antibiotic overuse: a key driver of antimicrobial resistance. *Br J Gen Pract*. 2014;64(629):604-605. https://doi.org/10.3399/bjgp14X682561.

141 Wang G, Li X, Wang Z. APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res*. 2016;44(D1):D1087-1093. https://doi.org/10.1093/nar/gkv1278.

142 Luo Y, Song Y. Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities. *Int J Mol Sci*. 2021;22(21):11401. https://doi.org/10.3390/ijms222111401.

143 Kang HK, Kim C, Seo CH, et al. The therapeutic applications of antimicrobial peptides (AMPs): a patent review. *J Microbiol*. 2017;55(1):1-12. https://doi.org/10.1007/s12275-017-6452-1.

144 Hancock RE, Nijnik A, Philpott DJ. Modulating immunity as a therapy for bacterial infections. *Nat Rev Microbiol*. 2012;10(4):243-254. https://doi.org/10.1038/nrmicro2745.

145 Epand RM, Walker C, Epand RF, et al. Molecular mechanisms of membrane targeting antibiotics. *Biochim Biophys Acta*. 2016;1858(5):980-987. https://doi.org/10.1016/j.bbamem.2015.10.018.

146 Khamlek S, Lucksiri A, Sunkonkit K, et al. Treatment outcomes and associated factors of intravenous colistin for nosocomial infections in pediatric patients: a retrospective study in a university hospital in Thailand. *Pediatr Infect Dis J*. 2024;Online ahead of print. https://doi.org/10.1097/INF.0000000000004450.

147 Gkartziou F, Plota M, Kypraiou C, et al. Daptomycin liposomes exhibit enhanced activity against staphylococci biofilms compared to free drug. *Pharmaceutics*. 2024;16(4):459. https://doi.org/10.3390/pharmaceutics16040459.

148 Wang P, Liu S, He X, et al. Therapeutic drug monitoring of polymyxin B cerebrospinal fluid concentrations in patients with carbapenem-resistant Gram-negative bacteria-induced central nervous system infection. *J Antimicrob Chemother*. 2024;79(8):1969-1973. https://doi.org/10.1093/jac/dkae193.

149 Browne K, Chakraborty S, Chen R X, et al. A new era of antibiotics: the clinical potential of antimicrobial peptides. *Int J Mol Sci*. 2020;21(19):7047. https://doi.org/10.3390/ijms21197047.

150 Lo SC, Xie ZR, Chang KY. Structural and functional enrichment analyses for antimicrobial peptides. *Int J Mol Sci*. 2020;21(22):8783. https://doi.org/10.3390/ijms21228783.

151 Silva ARP, Guimaraes MS, Rabelo J, et al. Recent advances in the design of antimicrobial peptide conjugates. *J Mater Chem B*. 2022;10(19):3587-3600. https://doi.org/10.1039/D1TB02757C.

152 Bechinger B, Gorr SU. Antimicrobial peptides: mechanisms of action and resistance. *J Dent Res*. 2017;96(3):254-260. https://doi.org/10.1177/0022034516679973.

153 Provias J, Jeynes B. The role of the blood-brain barrier in the pathogenesis of senile plaques in Alzheimer's disease. *Int J Alzheimers Dis*. 2014;2014:191863. https://doi.org/10.1155/2014/191863.

154 Gasca-Salas C, Fernandez-Rodriguez B, Pineda-Pardo JA, et al. Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. *Nat Commun*. 2021;12(1):779. https://doi.org/10.1038/s41467-021-21022-9.

155 Nishihara H, Perriot S, Gastfriend BD, et al. Intrinsic blood-brain barrier dysfunction contributes to multiple sclerosis pathogenesis. *Brain*. 2022;145(12):4334-4348. https://doi.org/10.1093/brain/awac019.

156 Falco-Walter J. Epilepsy-definition, classification, pathophysiology, and epidemiology. *Semin Neurol*. 2020;40(6):617-623. https://doi.org/10.1055/s-0040-1718719.

157 Armiento V, Spanopoulou A, Kapurniotu A. Peptide-based molecular strategies to interfere with protein misfolding, aggregation, and cell degeneration. *Angew Chem Int Ed Engl*. 2020;59(9):3372-3384. https://doi.org/10.1002/anie.201906908.

158 Liu KM, Lin HH, Pi RB, et al. Research and development of anti-Alzheimer's disease drugs: an update from the perspective of technology flows. *Expert Opin Ther Pat*. 2018;28(4):341-350. https://doi.org/10.1080/13543776.2018.1439475.

159 Balestrino R, Schapira AHV. Parkinson disease. *Eur J Neurol*. 2020;27(1):27-42. https://doi.org/10.1111/ene.14108.

160 Shen J, Zha Q, Yang QH, et al. Inhibiting von Hippel–Lindau protein-mediated dishevelled ubiquitination protects against experimental parkinsonism. *Acta Pharmacol Sin*. 2023;44(5):940-953. https://doi.org/10.1038/s41401-022-01014-1.

161 Yao SY, Wang JF, Xu Z, et al. A peptide rich in glycine-serine-alanine repeats ameliorates Alzheimer-type neurodegeneration. *Br J Pharmacol*. 2023;180(14):1878-1896. https://doi.org/10.1111/bph.16048.

162 Liu MC, Yang SJ, Yang JP, et al. Neuroprotective and memory-enhancing

effects of antioxidant peptide from walnut (*Juglans regia* L.) protein hydrolysates. *Nat Prod Commun*. 2019;14(7):1-13. https://doi.org/10.1177/1934578X19865838.

163 Zhang S, Asghar S, Zhu C, et al. Multifunctional nanorods based on self-assembly of biomimetic apolipoprotein E peptide for the treatment of Alzheimer's disease. *J Control Release*. 2021;335:637-649. https://doi.org/10.1016/j.jconrel.2021.05.044.

164 Guo Q, Xu S, Yang P, et al. A dual-ligand fusion peptide improves the brain-neuron targeting of nanocarriers in Alzheimer's disease mice. *J Control Release*. 2020;320:347-362. https://doi.org/10.1016/j.jconrel.2020.01.039.

165 Gentilucci L, De Marco R, Cerisoli L. Chemical modifications designed to improve peptide stability: incorporation of non-natural amino acids, pseudo-peptide bonds, and cyclization. *Curr Pharm Des*. 2010;16(28):3185-3203. https://doi.org/10.2174/138161210793292555.

166 Cheng JJ, Zhou JL, Kong LY, et al. Stabilized cyclic peptides as modulators of protein-protein interactions: promising strategies and biological evaluation. *Rsc Med Chem*. 2023;14(12):2496-2508. https://doi.org/10.1039/D3MD00487B.

167 Nattel S, Carlsson L. Innovative approaches to anti-arrhythmic drug therapy. *Nat Rev Drug Discov*. 2006;5(12):1034-1049. https://doi.org/10.1038/nrd2112.

168 Zhang L, Shan X, Meng X, et al. Novel integrin alphavbeta3-specific ligand for the sensitive diagnosis of glioblastoma. *Mol Pharm*. 2019;16(9):3977-3984. https://doi.org/10.1021/acs.molpharmaceut.9b00602.

169 Sagan S, Karoyan P, Lequin O, et al. *N*- and Calpha-methylation in biologically active peptides: synthesis, structural and functional aspects. *Curr Med Chem*. 2004;11(21):2799-2822. https://doi.org/10.2174/0929867043364108.

170 Cardillo G, Gentilucci L, Qasem AR, et al. Endomorphin-1 analogues containing beta-proline are mu-opioid receptor agonists and display enhanced enzymatic hydrolysis resistance. *J Med Chem*. 2002;45(12):2571-2578. https://doi.org/10.1021/jm011059z.

171 Toniolo C, Crisma M, Formaggio F, et al. Structures of peptides from alpha-amino acids methylated at the alpha-carbon. *Biopolymers*. 1993;33(7):1061-1072. https://doi.org/10.1002/bip.360330708.

172 Haskell-Luevano C, Toth K, Boteju L, et al. beta-Methylation of the Phe7 and Trp9 melanotropin side chain pharmacophores affects ligand-receptor interactions and prolonged biological activity. *J Med Chem*. 1997;40(17):2740-2749. https://doi.org/10.1021/jm970018t.

173 Ando M, Fujimoto M, Takahashi Y, et al. Targeted delivery of interferon gamma using a recombinant fusion protein of a fibrin clot-binding peptide with interferon gamma for cancer gene therapy. *J Pharm Sci*. 2017;106(3):892-897. https://doi.org/10.1016/j.xphs.2016.11.018.

174 Karimi M, Ghasemi A, Sahandi ZP, et al. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. *Chem Soc Rev*. 2016;45(5):1457-1501. https://doi.org/10.1039/C5CS00798D.

175 Moldaver D, Larche M. Immunotherapy with peptides. *Allergy*. 2011;66(6):784-791. https://doi.org/10.1111/j.1398-9995.2011.02610.x.

176 Guo F, Zhang MY, Gao Y, et al. Modified nanoparticles with cell-penetrating peptide and amphipathic chitosan derivative for enhanced oral colon absorption of insulin: preparation and evaluation. *Drug Deliv*. 2016;23(6):2003-2014. https://doi.org/10.3109/10717544.2015.1048489.

177 Yang MY, Lin YJ, Han MM, et al. Pathological collagen targeting and penetrating liposomes for idiopathic pulmonary fibrosis therapy. *J Control Release*. 2022;351:623-637. https://doi.org/10.1016/j.jconrel.2022.09.054.