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# Peptide-based therapeutic and delivery strategies for inflammatory bowel disease: challenges and future directions

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Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), remains a challenging chronic disorder with complex pathophysiology and limited therapeutic options. Peptide-based therapeutics have emerged as promising alternatives, offering high specificity, favorable safety profiles, and unique biological activities compared to traditional treatments. However, challenges including enzymatic degradation, poor oral bioavailability, and instability hinder their clinical translation. This review provides a comprehensive overview of the sources, structures, and mechanisms of therapeutic peptides for IBD management. We further discuss recent advances in delivery strategies, including PEGylation, nanoparticle (NP) systems (chitosan (CS), hyaluronic acid (HA), PLGA, lipid-based carriers, polydopamine (PDA), mesoporous materials), hydrogels, engineered probiotics, and montmorillonite-based composites. Particular emphasis is placed on the role of biomaterials in enhancing peptide stability, targeting specificity, and mucosal adhesion. Key challenges—such as optimizing peptide design, ensuring biosafety, refining delivery systems, and improving preclinical models—are critically analyzed. Prospects suggest that combining smart delivery technologies with data-driven peptide engineering will significantly advance peptide-based therapies for precision IBD management.

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## 1. Introduction

Inflammatory bowel disease (IBD) refers to chronic inflammatory disorders of the gastrointestinal (GI) tract, primarily consisting of two subtypes: ulcerative colitis (UC) and Crohn's disease (CD).[1] As an immune-mediated condition, IBD involves persistent inflammation with varying phenotypic presentations. CD manifests as discontinuous, transmural inflammation affecting any segment of the GI tract, extending from the oral cavity to the anal region. In contrast, UC presents as a continuous, mucosal-limited inflammatory process exclusively involving the colorectum. IBD poses a significant global health challenge, affecting about 1 million people in the United States and 2.5 million across Europe.[2] Recent epidemiological studies show its expanding reach, with rising prevalence in traditionally low-incidence regions such as Asia, South America, and the Middle East. This shift from primarily western countries to global distribution highlights IBD's emergence as a worldwide health concern affecting all inhabited continents.[2,3] IBD is characterized by chronic GI symptoms, including abdominal pain, persistent diarrhea, and hematochezia. Systemic effects often involve weight loss, iron-deficiency anemia, and fever. Additionally, extraintestinal manifestations (*e.g.*, fatigue, depression, anxiety) are common and may coexist with ankylosing spondylitis.[4,5] These diverse symptoms collectively impair patients' quality of life and functional capacity. The

precise etiology of IBD remains elusive, though evidence points to interconnected factors including genetic predisposition, immune dysfunction, environmental influences, and intestinal microbiome alterations.[6]

Currently, no cure exists for IBD, and treatment focuses on achieving and sustaining remission of inflammatory flares.[7] The primary objective of IBD treatment is to suppress the aberrant immune-inflammatory response and achieve sustained clinical remission. Current therapeutic approaches encompass conventional medications, including aminosalicylates, corticosteroids, and immunomodulators; biologic agents targeting tumor necrosis factor (TNF), integrins, and interleukins; and small-molecule drugs such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) modulators. Emerging therapies, including anti-IL-23 agents, TL1A inhibitors, and receptor-interacting protein kinase 1 (RIPK1) inhibitors, offer novel, targeted strategies to modulate inflammation, thereby expanding the therapeutic landscape and providing new options for patients with IBD.[8–11] Since IBD is a multifactorial disease, non-pharmacological strategies play a complementary role alongside drug therapies. These include maintaining a healthy diet, engaging in regular physical exercise, weight management, smoking cessation, and mental health support.[12–16] Patients with IBD should select treatments that align with their lifestyle. Multidisciplinary care is essential, requiring collaboration among clinicians, nurses, and patients themselves to effectively manage the disease and minimize relapses.[8,17]

Current therapeutic approaches for IBD, including conventional medications and biological agents, present several significant clinical limitations. Conventional therapies such as corticosteroids and immunomodulators often exhibit limited treatment support.[12–16] Patients with IBD should select treatments that align with their lifestyle. Multidisciplinary care is essential, requiring collaboration among clinicians, nurses, and patients themselves to effectively manage the disease and minimize relapses.[8,17]

Current therapeutic approaches for IBD, including conventional medications and biological agents, present several significant clinical limitations. Conventional therapies such as corticosteroids and immunomodulators often exhibit limited treatment specificity, potentially leading to systemic adverse effects while requiring progressively increased dosages to maintain efficacy.[18] The compromised immune function associated with these treatments frequently results in drug-class-related complications, particularly severe infections. Furthermore, while biological agents targeting specific inflammatory pathways have demonstrated promising clinical outcomes, approximately 30–50% of patients either fail to respond initially or develop neutralizing antibodies that diminish therapeutic effectiveness over time.[19] These treatment drawbacks collectively highlight the urgent need for more precise and sustainable therapeutic strategies in IBD management.

Therapeutic peptides have gained significant attention in the biomedical field due to their safety and bioactive properties.[20] Peptide-based therapeutics offer distinct advantages over conventional drugs, including high target specificity, enhanced safety profiles with minimal off-target effects, and low immunogenicity.[21,22] Additionally, peptide manufacturing is more cost-effective than conventional drug production, presenting a promising approach to overcome the limitations of traditional small molecules and biologics.[23,24] With nearly 100 approved peptide drugs worldwide and numerous compounds advancing from preclinical to clinical trials, the peptide therapeutics market continues to expand rapidly.[25] While peptide therapeutics have advanced significantly, developing effective IBD treatments still faces key pharmacological challenges, particularly for oral delivery. The harsh GI environment promotes enzymatic degradation and poor absorption, necessitating subcutaneous injections, which compromise patient adherence. Exciting innovations in peptide engineering – including cyclization and modified amino acids – combined with advanced delivery systems like mucus-penetrating nanoparticles (NPs) and targeted colonic release technologies now offer solutions.[26] These approaches show promise for creating stable, bioavailable oral peptide formulations that could revolutionize IBD treatment by maintaining efficacy while greatly improving patient compliance.

Recent discussions have highlighted the potential of peptides for IBD treatment. Qiu *et al.* systematically examined food-derived peptides with anti-IBD properties, analyzing their amino acid sequences, physicochemical characteristics, and biological mechanisms.[27] Another study provides a comprehensive review of immunologically active peptides, focusing specifically on their role in intestinal inflammation.[28] These works illuminate peptide applications in IBD therapy. In this review, we will update current findings on food-derived peptides for IBD treatment while also examining other peptide sources. We will analyze their targets in IBD pathophysiology, with

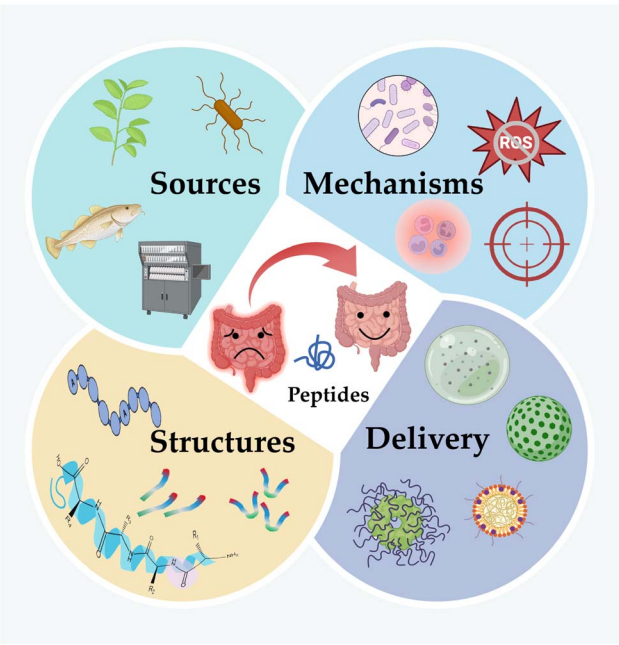



Fig. 1 Peptides in IBD therapy: from sources and structural to mechanistic insights and advanced delivery strategies.

Table 1 Peptides for IBD treatment[a]

| Name | Source | Sequence | Mechanisms | Delivery approach | Ref. |
|---|---|---|---|---|---|
| Various binding/ targeting peptides | Synthetic | YGRRARRRARR; YGRKKRRQRRR; AAVALLPAVLLALLAP; TALDWSWLQTE; VQRKRQKLMP; QLRRPSDRELSE | Colon-targetability, enhanced cell permeability for effective delivery, and inhibition of NFκB activity, which plays a crucial role in regulating immunity and inflammation | Oral | 38 |
| S100A8/9 peptide CT peptide | Synthetic | FLVIK–GG–ITITF–GG–AHKSHK–GG—GHHGG; TWYKIAFQRNRK | Inhibition of TLR4- and RAGE-mediated signaling, thereby reducing colonic inflammation and IBD severity. Colon-targetability | Intraperitoneal (IP) | 39 |
| NIPEPIM-0127 | Synthetic | — | Recovery of inflammatory cytokine levels through the inhibition of immune complex formation | Oral | 40 |
| V-type peptide liner peptide | Synthetic | DFFGCGFFDDFFKCDFFD | Inhibition of endosomal TLR signaling; modulation of macrophage polarization | IP | 41 |
| RDP58 | Synthetic | D(R-nnnR-nnnGY-$NH_2$) | Altering the diversity and composition of intestinal microbiota | Oral | 42 |
| Pe | Synthetic | QRMRELTV | Peptide-guided adhesion to TLR5 and Notch-1; suppression of inflammatory signaling *via* TNF-α | Intestinal injection | 43 |
| C Domain peptide | Synthetic | GYGSSSRRAPQT | Enhanced hP-MSC engraftment, alleviated inflammation, and promoted colitis recovery *via* PGE2-mediated M2 macrophage polarization | Intestinal injection | 44 |
| P140 | Synthetic | RIHMVYSKRpSGKPRGYAFIEY | Corrected autophagy defects in colon and spleen tissues of colitis mice | Intravenously (IV) | 45 |
| Casein phosphopeptide (CPP) | Synthetic | pSpSpSEE | Scavenge ROS, promote crypt regeneration, alleviate inflammation, and enable targeted IBD treatment | Oral | 46 |
| P-selectin binding peptide (PBP) | Synthetic | — | Binding to P-selectin to reduce inflammation | i.v. | 47 |
| Ac2-26 | Synthetic | AMVSEFLKQAWFIENEEQEYVQTVK | Anti-inflammatory | Oral | 48 |
| mCRAMP | Synthetic | GLLRKGGEKIGEKLKKIG-QKIKNFFQKLVPQPEQ | Reduced pro-inflammatory cytokines, elevated anti-inflammatory cytokines, enhanced targeting to inflamed tissues, and optimized intestinal microbiome | Oral | 49 |
| M27-39 | *Musca domestica cecropin* | VAQQAANVAATLK | Colon-targetability; cell permeability to enhance drug delivery | Oral | 50 |
| Biopeptides | *Lupinus mutabilis* seeds | — | Antioxidant capacity | — | 51 |
| Sea conch peptide hydrolysate (CPH) | Sea conch | — | Decreased pro-inflammatory cytokines, increased anti-inflammatory cytokines, modulation of NF-κB pathway, reduced oxidative DNA damage and apoptosis | Oral | 52 |
| Sturgeon-derived peptide | Sturgeon | LLLE | Improved colon morphology, reduced serum IL-6, modulation of gut microbiota and restoration of anti-inflammatory metabolites | Oral | 53 |
| Vasoactive intestinal peptide (VIP) | Endogenous | HSDAVFTDNYTRLRK-QMAVKKYLNSILN | Anti-inflammatory and antidiarrheal effects | IP | 54 |
| Neuropeptide Y (NPY) | Endogenous | YPSKPDNPGEDAPSA-APGRSLSSSRIKRGF | Immunoregulatory ability | — | 55 |

Table 1 (*Contd.*)

| Name | Source | Sequence | Mechanisms | Delivery approach | Ref. |
|---|---|---|---|---|---|
| αs2-casein | *Lactobacillus gasseri 505* | VYQHQKAMKPW-IQPKTKVIPYVRYL | Anti-inflammatory effects | Oral | 56 |
| Peptide B7 | *Bifidobacterium longum* subsp. *longum* | WIEAVGYSLTQHPDPELEK | Regulate host immune responses, stimulate tolerogenic dendritic cells, induce Treg responses, and exert immunosuppressive and anti-inflammatory effects | — | 57 |

[a] "—" indicates that the information was not provided in the original source.

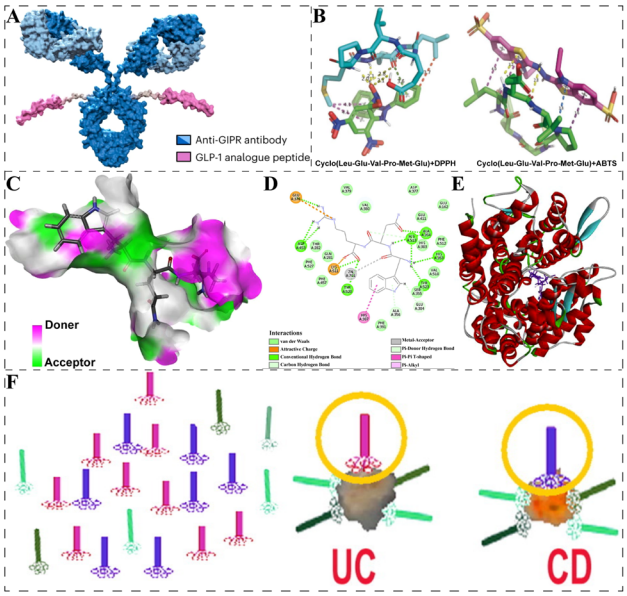



Fig. 2 (A) Structural representation of the GIPR–GLP-1 conjugate molecule. Reproduced from ref. 60 with permission from Springer Nature, copyright 2024. (B) Molecular docking of cyclic peptides with DPPH and ABTS free radicals, demonstrating their antioxidant potential. Reproduced from ref. 62 with permission from Elsevier Ltd, copyright 2025. (C) Three-dimensional surface plot of hydrogen bonding interactions at the binding site of the Trp–Gln–Arg (WQR) peptide. Reproduced from ref. 67 with permission from Elsevier Ltd, copyright 2020. (D) Illustration of ACE and WQR molecular interaction. Reproduced from ref. 67 with permission from Elsevier Ltd, copyright 2020. (E) Predicted 3D structure of the ACE-WQR complex. Reproduced from ref. 67 with permission from Elsevier Ltd, copyright 2020. Reproduced from ref. 67 with permission from Elsevier Ltd, copyright 2020. (F) Identification of UC- or CD-specific binding peptides using display screening methods. Reproduced from ref. 76 with permission from Elsevier Ltd, copyright 2017.

particular emphasis on delivery strategies. Finally, we will discuss future perspectives on peptide-based IBD therapies (Fig. 1).

## 2. Overview of peptides

The U.S. Food and Drug Administration (FDA) defines a peptide as an amino acid polymer comprising fewer than 40 residues, typically ranging from 500 to 5000 Da in molecular weight.[29] These chains, formed *via* amide bonds between diverse amino acid sequences, exhibit remarkable structural diversity and design flexibility.[30] As therapeutic agents, peptides occupy a unique intermediate position between small-molecule drugs and protein biologics. This distinct structural niche confers biochemical properties and therapeutic mechanisms that fundamentally differentiate peptides from both conventional drug classes.[31] Currently, more than 100 peptide-based drugs have been approved, and the number continues to rise as many peptides progress from preclinical studies to clinical trials.[25] Notably, the approval of semaglutide for diabetes treatment and weight loss, as well as tirzepatide for weight management, has demonstrated superior efficacy in the SURPASS phase III trials.

These groundbreaking advancements underscore the ongoing rapid progress in peptide drug development.[32–34]

In this review, we provide an updated summary of the work by Qiu *et al.*,[27] with a particular focus on recently identified peptides and their emerging applications in the management of IBD (Table 1).

## 3. Sources of peptides

Peptides, comprising both naturally occurring sequences and their synthetic analogs, are widely distributed across plant and animal organisms.[35] These peptides are typically released *via* enzymatic hydrolysis of dietary proteins within the GI tract, generating fragments that exert diverse and specific biological functions. They are involved in key physiological processes such as signal transduction, growth regulation, immune modulation, and maintenance of homeostasis.[36] While endogenous peptides primarily exert their effects within the host organism, some retain bioactivity when administered exogenously.[37]

However, peptides derived from mammalian tissues and synthetic sources often encounter pharmacokinetic limitations, including rapid degradation, short plasma half-life, and poor oral bioavailability.

To overcome these challenges, researchers have developed engineered peptide analogs through targeted structural modifications, such as amino acid substitutions and conjugation strategies.[58,59] A representative example is the development of glucagon-like peptide-1 (GLP-1) receptor agonists. Recent advances have introduced a bispecific molecule comprising a fully human monoclonal anti-glucose-dependent insulinotropic polypeptide receptor (GIPR) antibody conjugated to two GLP-1 analog peptides *via* optimized amino acid linkers.[60] This construct has demonstrated enhanced clinical efficacy, including significant weight reduction and an improved safety and tolerability profile (Fig. 2A).

### 3.1. Plant-derived peptides

Plant-derived peptides represent a substantial resource for biomedical applications, offering cost-effective and sustainable alternatives that have attracted considerable research interest. Scientists have identified over 1500 distinct modified peptides from plants, exhibiting remarkable diversity in molecular size, chemical structure, and biological activity.[61] These compounds originate from plants' natural defense systems, which produce systemic response proteins and antimicrobial agents in response to environmental stresses. Recent studies have successfully isolated potent antioxidant cyclic peptides from plants and synthesized analogous compounds, providing valuable insights for novel therapeutic development (Fig. 2B).[62] Other research has demonstrated the antidiabetic, anti-obesity, and antioxidant properties of flaxseed and chia seed peptides, showing their potential to regulate blood glucose and cholesterol levels.[63]

The growing market for plant-based protein beverages has spurred investigations into their bioactive components. Researchers have characterized amaranth protein-derived peptides with significant antihypertensive, antioxidant, and antithrombotic effects, including enhanced angiotensin I-converting enzyme (ACE) inhibition, fibrin clot prevention, and free radical scavenging capacity.[64] In a comprehensive review, Zaky *et al.* systematically examined plant-derived peptides, covering extraction techniques to therapeutic applications, thereby summarizing current progress in this field.[65]

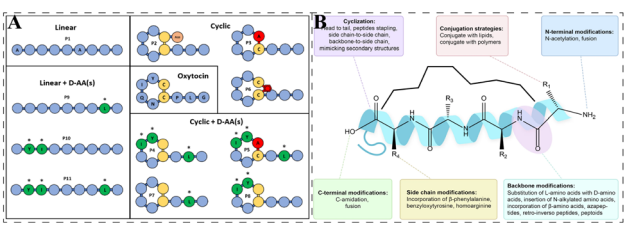



Fig. 3 (A) Schematic structures of oxytocin and its derivatives, including linear and cyclic variants. Reproduced from ref. 85 with permission from MDPI, copyright 2023. (B) Various strategies to improve the physicochemical properties of peptides. Reproduced from ref. 86 with permission from Springer Nature, copyright 2025.

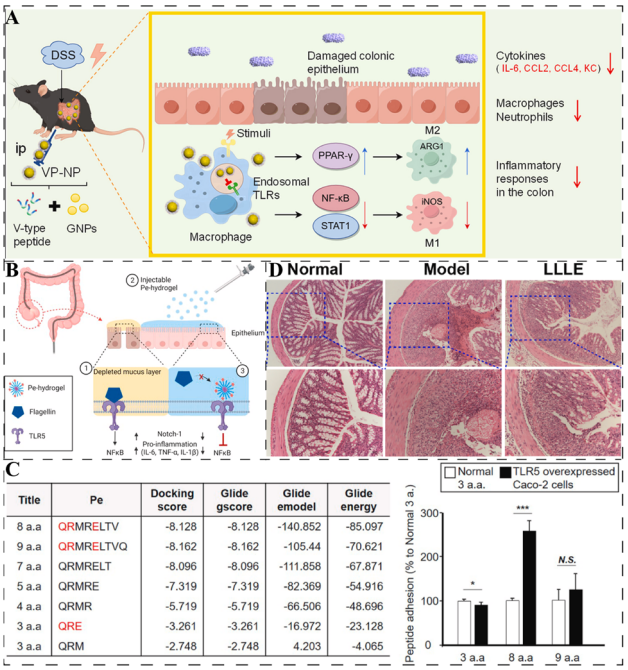
### 3.2. Marine peptides

The exceptional biodiversity of marine macro- and microorganisms has established oceans as a key source of bioactive molecules, with marine-derived peptides demonstrating unique structural characteristics and diverse bioactive functions such as enhanced bioavailability, reduced toxicity, and greater biocompatibility compared to terrestrial counterparts.[66]

A notable example is marine ACE inhibitory peptides, which play a crucial role in blood pressure regulation and show promise for improving cardiovascular disease outcomes (Fig. 2C).[67,68] The binding sites of the WQR peptide with ACE are clearly illustrated in Fig. 2D, and the 3D structure of the ACE–WQR complex was predicted using Discovery Studio R2 Client (Fig. 2E). The calculated CDOCKER energy was $-98.5874$ kcal mol$^{-1}$, demonstrating a strong binding affinity between the peptide and ACE. Multiple marine peptides have been confirmed as effective ACE inhibitors, with the added advantage of fewer adverse effects than synthetic alternatives.[69] Another significant discovery is C-phycocyanin (C-PC), a water-soluble protein obtained from cyanobacteria, red algae, and select cryptomonads, which exhibits potent anti-inflammatory properties.[70] Research has specifically identified bioactive peptides derived from C-PC with significant activity against IBD. When synthesized and tested in an IBD zebrafish model, these peptides demonstrated strong anti-inflammatory effects, underscoring their potential as a novel therapeutic foundation for IBD treatment. These findings collectively highlight the immense therapeutic potential of marine-derived peptides, particularly in addressing complex inflammatory disorders.

### 3.3. Microbial-derived peptides

Microorganisms, particularly probiotics, play a critical role in enhancing human health by improving nutrient absorption, synthesizing essential vitamins, and producing antimicrobial




| Title | Pe | Docking score | Glide gscore | Glide emodel | Glide energy |
|---|---|---|---|---|---|
| 8 a.a | QRMRELTV | -8.128 | -8.128 | -140.852 | -85.097 |
| 9 a.a | QRMRELTVQ | -8.162 | -8.162 | -105.44 | -70.621 |
| 7 a.a | QRMRELT | -8.096 | -8.096 | -111.858 | -67.871 |
| 5 a.a | QRMRE | -7.319 | -7.319 | -82.369 | -54.916 |
| 4 a.a | QRMR | -5.719 | -5.719 | -66.506 | -48.696 |
| 3 a.a | QRE | -3.261 | -3.261 | -16.972 | -23.128 |
| 3 a.a | QRM | -2.748 | -2.748 | 4.203 | -4.065 |

Fig. 4 (A) VP-NP alleviates colitis through anti-inflammatory mechanisms. Reproduced from ref. 41 with permission from Elsevier Ltd, copyright 2025. (B) Injectable hydrogel administered *via* syringe retains intestinal moisture and binds to TLR5 overexpressed during inflammation. Reproduced from ref. 43 with permission from Elsevier Ltd, copyright 2022. (C) The binding efficiency of peptide candidates to TLR5 was assessed by comparing adhesion to Caco-2 cells before and after TLR5 overexpression induced by inflammation. Reproduced from ref. 43 with permission from Elsevier Ltd, copyright 2022. (D) LLLE treatment significantly reduces crypt damage, inflammatory cell infiltration, and histological scores. Reproduced from ref. 53 with permission from Elsevier Ltd, copyright 2024.

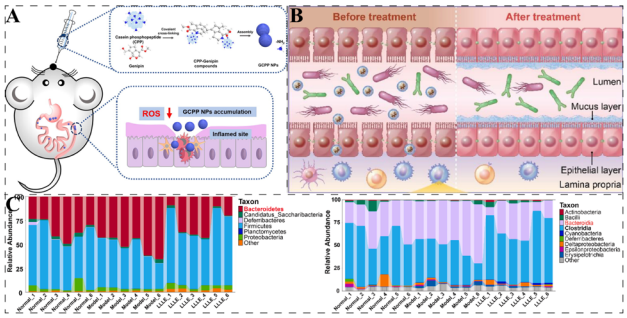



Fig. 5 (A) GCPP nanoparticles, formed *via* covalent cross-linking of CCP and genipin, accumulate in inflamed sites for ROS scavenging in IBD therapy. Reproduced from ref. 46 with permission from Elsevier Ltd, copyright 2022. (B) mCRAMP nanoparticles mitigate IBD by promoting beneficial bacteria and inhibiting pathogenic microbial communities. Reproduced from ref. 49 with permission from Elsevier Ltd, copyright 2023. (C) LLLE reverses IBD-associated dysbiosis by increasing *Firmicutes* and reducing *Bacteroidetes* at both phylum and class levels. Reproduced from ref. 53 with permission from Elsevier Ltd, copyright 2024.

metabolites that protect against pathogenic organisms.[71] Specific probiotic strains have been shown to enhance immunomodulatory effects by regulating the mucosal immune system, thereby providing sustained health benefits. Moreover, probiotic supplementation offers a cost-effective, safe, and noninvasive strategy to mitigate the adverse consequences of antibiotic-induced gut microbiota disruption.[72]

Recent research on *Enterococcus faecium* OV3-6 highlights its remarkable heat stability, acid resistance, and thermal tolerance—properties that make its derived bioactive peptides particularly suitable for industrial food applications.[73] Lactic acid bacteria fermentation, especially using *Lactobacillales*, provides an efficient biotechnological platform for bioactive peptide production. Notably, starter cultures such as *Lactococcus lactis*, *Lactobacillus helveticus*, and *Lactobacillus delbrueckii* subsp. *bulgaricus* demonstrates highly effective proteolytic systems capable of releasing bioactive peptides from milk proteins.[74,75]

### 3.4. Synthetic peptide production and rational design approaches

Another source of peptides, distinct from naturally occurring peptides, can be obtained through synthetic libraries, phage display, and other synthetic methods.[31] One study developed a novel diagnostic approach to differentiate between UC and CD by utilizing phage display-derived peptides combined with virus-mimicking synthetic NPs (Fig. 2F).[76] In peptide engineering, researchers employ multiple rational design strategies to achieve targeted biological properties. For example, in the development of AMPs, these strategies generally fall into two categories: systematic modification of naturally occurring AMPs and *de novo* design of novel synthetic peptides. Both approaches require comprehensive structural characterization and a thorough evaluation of biological activities.

The primary goal of peptide design is to optimize therapeutic efficacy by simultaneously enhancing bioactivity and minimizing cytotoxicity. To this end, various structure–activity relationship (SAR) methodologies are employed, including, but not limited to, site-directed mutagenesis, rational computational design, high-throughput screening of synthetic peptide libraries, template-guided structural refinement, and mechanism-driven design strategies inspired by natural biological processes.[77] Each technique offers unique advantages for elucidating the critical structural determinants that govern antimicrobial activity and toxicity profiles.[78]

The emergence of artificial intelligence (AI), machine learning, and deep learning has revolutionized peptide design, placing these technologies at the forefront of computational approaches.[79] Advanced computational tools now enable rapid prediction and optimization of peptide sequences with desired bioactivities, providing unprecedented opportunities for accelerating peptide discovery and development. By analyzing vast datasets of peptide sequences and their associated biological properties, AI-driven algorithms can identify novel design rules, predict structure–activity relationships, and generate optimized candidates with enhanced therapeutic potential while minimizing undesirable characteristics. This paradigm shift in

peptide engineering combines data-driven insights with traditional rational design principles, substantially expanding the landscape of feasible peptide therapeutics.[80] Recently, researchers developed a long short-term memory (LSTM) model for designing therapeutic peptides. Rather than relying on predefined physicochemical features such as charge or hydrophobicity, LSTM architectures are typically trained solely on primary sequence data to capture contextual and sequential dependencies within peptides. As such, these models do not directly provide residue-level physicochemical insights, but instead focus on generating novel sequences that can later be screened through additional layers such as molecular docking, dynamics simulations, or experimental validation.[81]

## 4. Structures of peptides

Peptide sequence and structure critically determine bioactivity, with similar sequences often exhibiting analogous functions.[82] For example, the key factors influencing AMP activity include specific amino acid residues, net charge, hydrophobicity, amphipathicity, and structural characteristics.[83] Sequence alterations, variations in peptide length, and changes in net charge can significantly affect hydrophobicity, wherein both positive charge and hydrophobicity are essential for antibacterial function.

In the treatment of IBD, therapeutic peptides are predominantly small molecules, typically comprising 2–10 amino acids, with 3–8 residues being most common—a length that likely facilitates intestinal transport *via* peptide transporters while minimizing enzymatic degradation.[83] Peptide activity is primarily influenced by modifications at the N- and C-termini. Critical immune responses are modulated by residues such as phenylalanine (F), tyrosine (Y), and proline (P).[84] In IBD-related peptides, the most frequent N-terminal amino acids are leucine (L), serine (S), glutamate (E), and glycine (G), while arginine (R) and phenylalanine (F), followed by proline (P) and leucine (L), are predominant at the C-terminus.[27]

Furthermore, one study enhanced peptide stability and colonic permeability through disulfide bond cyclization and D-amino acid substitutions at tyrosine, isoleucine, and leucine residues (Fig. 3A).[85] This was the first study to systematically link peptide secondary structure alterations—achieved *via* D-amino acid substitutions—to improved colonic delivery, offering a promising strategy for the oral administration of peptide therapeutics targeting colon-specific diseases such as IBD. Xiao *et al.* also summarized strategies aimed at improving the physicochemical properties of peptides, including novel design techniques such as display libraries, AI-assisted screening, and structural modifications, to overcome challenges like rapid clearance and enzymatic degradation (Fig. 3B).[86] Advanced structural and functional analyses, especially when combined with AI and deep learning technologies, are expected to further accelerate the precise prediction and rational design of therapeutic peptides, thereby expanding their clinical applicability in diseases such as IBD.

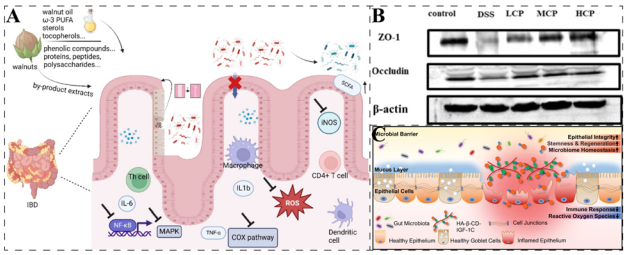



Fig. 6 (A) Mechanisms of walnut extract in IBD regulation include mucosal barrier repair, ROS scavenging, and microbiota balance. Reproduced from ref. 100 with permission from MDPI, copyright 2024. (B) Sea conch-derived peptides upregulate tight junction proteins ZO-1 and occludin. Reproduced from ref. 52 with permission from Wiley-VCH GmbH, copyright 2024. (C) Biomimetic supramolecular structures exhibit anti-inflammatory and ROS-inhibitory effects while promoting gut microbiota regeneration. Reproduced from ref. 102 with permission from Wiley-VCH GmbH, copyright 2024.

## 5. Peptides targeting IBD pathophysiology

Previous research has systematically classified peptides with diverse therapeutic functions for IBD treatment.[27,28] Our comprehensive review of existing studies demonstrates that most peptides exhibit multiple beneficial effects, particularly when integrated with advanced delivery platforms. For optimal IBD therapy, current peptide development focuses on three key parameters: potent anti-inflammatory mechanisms, precise intestinal targeting capabilities, and clinical efficacy of peptide-based therapies.

To facilitate understanding of peptide multifunctionality, we have organized the existing literature according to peptide function.

### 5.1. Anti-inflammatory effects of peptides for IBD

Substantial progress has been made in developing peptides with potent anti-inflammatory properties—considered the most critical characteristic for effective IBD treatment.

Excessive Toll-like receptor (TLR) activation contributes significantly to IBD pathogenesis, making TLR inhibition a promising therapeutic strategy. In one study, researchers engineered a V-shaped peptide NP complex (VP-NP) with anti-inflammatory properties through TLR pathway inhibition (Fig. 4A).[41] This peptide featured dual FFD motifs as arms and a central cysteine residue. The phenylalanine (FF) residues facilitated macrophage uptake of LP-NP, while the negatively charged aspartate (D) residues prevented endosomal acidification. The transcriptomic analysis confirmed that LP-NP down-regulated multiple inflammatory pathways—including NF-κB, JAK-STAT, TNF, TLR, and cytokine/chemokine signaling—demonstrating strong anti-inflammatory effects in IBD.

Another mechanism involves TLR5 overexpression triggered by the *Bacillus subtilis* flagellin D1 domain, which promotes inflammatory activation.[87] As the D1 domain is a conserved binding site, it serves as an ideal therapeutic target. Researchers used computer simulations to design an 8-amino acid peptide

that mimics flagellin for TLR5 binding (Fig. 4B).[43] The TLR5 structure was sourced from the Protein Data Bank (PDB), pre-processed using the Protein Preparation Wizard, and analyzed through molecular docking and molecular mechanics generalized born surface area (MM-GBSA) binding energy calculations. The binding affinities of peptide candidates were evaluated using the Schrödinger software suite. As shown in Fig. 4C, the predicted interaction modes between the peptides and the target proteins involve multiple non-covalent forces, including hydrogen bonding, hydrophobic interactions, electrostatic interactions, van der Waals forces, and aromatic stacking.[88] These interactions collectively contribute to binding stability, and more negative energy values indicate stronger binding affinities. Among the tested sequences, the 8 a.a. and 9 a.a. peptides exhibited the most favorable binding scores. The binding efficiency of these peptides was further validated using immunoprecipitation (IP) followed by immunoblotting (IB) in TLR5-overexpressing human intestinal epithelial (Caco-2) cells. Ultimately, the 8 a.a. peptide was selected and incorporated into a sprayable hydrogel system, which effectively suppressed inflammation in the absence of any additional drug loading.

Additional anti-inflammatory peptide mechanisms have also been reported. A peptide system containing TLR4-and RAGE-inhibiting motifs was developed for colitis treatment, targeting two critical mediators of colonic inflammation.[39] Walnut-derived peptide LPLLR (LP-5) alleviated colitis by regulating autophagy and inflammasome activity *via* the AMPK/mTOR/ULK1 pathway.[89] Similarly, a sturgeon-derived peptide restored metabolites like indole-3-propionic acid, contributing to anti-inflammatory effects (Fig. 4D).[53] Peptides encoded in the human intestine or derived from synbiotics have also demonstrated significant anti-inflammatory properties.[56,57]

### 5.2. Antioxidant peptides for IBD treatment

The overproduction of ROS and reactive nitrogen species (RNS) damages cellular structures, promotes pro-inflammatory cytokine release, and accelerates IBD progression.[90] ROS overproduction is now recognized as a hallmark of IBD.[91]

Numerous bioactive peptides, particularly dietary peptides, exhibit potent antioxidant properties due to their superior intestinal absorption. Studies have demonstrated the redox-modulating effects of peptides derived from walnuts, eggs, rice, fish, soybeans, wheat, and milk. The Keap1-Nrf2 pathway serves as the primary antioxidant defense mechanism, maintaining redox homeostasis and mitigating oxidative stress.[92] Industrially produced rice protein peptides (RPP) have demonstrated protective effects against colitis by activating the Keap1-Nrf2 signaling pathway. These peptides enhance antioxidant enzyme expression and improve intestinal barrier integrity through upregulation of tight junction proteins.[93]

Additionally, researchers developed covalently assembled antioxidative peptide NPs (GCPP NPs) by combining genipin with CPP, which enhanced antioxidative capacity and stability under physiological conditions (Fig. 5A).[46] In a colitis model, GCPP NPs demonstrated significant therapeutic effects, including attenuated inflammation and improved colon tissue repair.

### 5.3. Regulating gut microbiota homeostasis

The GI tract is a complex ecosystem, where the intestinal epithelium interfaces with a diverse microbiota comprising roughly 100 trillion microorganisms.[94] Immune tolerance toward symbiotic microorganisms and defense against pathogens is critical for maintaining intestinal homeostasis. Disruption of this balance can initiate pathological cascades leading to IBD.[95]

AMPs, predominantly secreted by Paneth cells, are vital for gut homeostasis by controlling pathogenic and commensal bacterial populations.[96] For instance, Liu *et al.* utilized the antimicrobial peptide mCRAMP, a homolog of LL-37, to restore microbial equilibrium in IBD models (Fig. 5B).[49] Both *in vitro* and *in vivo* studies demonstrated its efficacy in reducing inflammation and correcting immune dysfunction. Similarly, RDP58, a peptide-based anti-inflammatory agent, improved colitis in mice by enhancing microbial diversity and promoting short-chain fatty acid (SCFA)-producing bacteria, which in turn stimulated regulatory T cell (Treg) differentiation—a critical anti-inflammatory mechanism.[42] In another study, LLLE peptides were shown to alleviate colitis symptoms, improve colon morphology, lower disease activity index (DAI) scores, and reduce IL-6 levels (Fig. 5C).[53] 16S rRNA sequencing revealed that LLLE altered gut microflora by decreasing *Bacteroidetes* populations and restoring beneficial metabolites like indole-3-propionic acid.

Collectively, these findings highlight the important role of peptides in modulating gut microbiota and maintaining intestinal immune homeostasis.

### 5.4. Targetability of peptides

Colon-targeted delivery is crucial for effective IBD therapy. However, oral administration of peptides faces significant challenges, including susceptibility to degradation by gastric acid and digestive enzymes, as well as issues related to patient compliance.[97]

Consequently, developing advanced strategies to achieve precise colonic release has become a major research focus.

Peptides, owing to their biocompatibility, chemical versatility, affordability, and selective binding capabilities, have emerged as promising candidates for colon-targeted delivery. For instance, a 12-residue peptide (TK), synthesized *via* solid-phase methods, was shown to bind effectively with integrin $\alpha 6\beta 1$ in colon cancer cells, highlighting its potential for targeted colonic therapies.[98] In addition, researchers have identified a colonic-targeting (CT) peptide that specifically binds to colon tissue, which was further conjugated to another peptide system for enhanced IBD treatment.[39,99] Another study employed RGD as an M-cell-targeting ligand to improve catalase encapsulation, exploiting ROS release associated with IBD. RGD conjugation significantly enhanced targeting efficiency, demonstrating its utility in peptide-based colon-specific therapies.

### 5.5. Other mechanisms

Structural damage to the colon in IBD leads to increased intestinal epithelial permeability, a hallmark feature of colitis.

Reducing mucosal permeability is therefore a critical strategy for promoting IBD healing by preventing antigen-induced colon injury. Studies have shown that walnut-derived peptides can protect the intestinal barrier and enhance mucosal integrity (Fig. 6A).[100] Similarly, sea conch-derived peptides have been reported to upregulate the expression of tight junction proteins, such as occludin and zonula occludens-1 (ZO-1), thereby strengthening the epithelial barrier (Fig. 6B).[52]

Insulin-like growth factor 1 (IGF-1) functions as both a pro-mitogenic factor and a macrophage-regulated protein, playing a crucial role in the immunomodulatory effects of mesenchymal stem cells (MSCs) and in maintaining intestinal crypt cell homeostasis.[101] In one study, researchers developed a biomimetic supramolecular assembly for the sustained delivery of the IGF-1C peptide (Fig. 6C).[102] This system not only enhanced the stability and prolonged the release of IGF-1C but also effectively reduced inflammation and restored intestinal barrier function.

Autophagy has also been implicated in IBD pathogenesis. In three distinct mouse models of colitis, the phosphopeptide P140—a 21-mer peptide—was shown to alleviate both clinical and histological disease severity.[45] This therapeutic effect was associated with the normalization of autophagy-related markers (macroautophagy and chaperone-mediated autophagy) and reduced expression of pro-inflammatory mediators.

Overall, peptide-based therapeutics exhibit multifaceted efficacy in IBD treatment. Their potent ROS-scavenging capacity not only confers anti-inflammatory effects but also facilitates the modulation of the gut microbiota to restore microbial homeostasis. This dual mechanism of action promotes enhanced intestinal mucosal repair. Furthermore, advanced delivery systems enable the precise accumulation of bioactive peptides at sites of colonic injury, significantly improving therapeutic precision. As research continues to unravel the complex pathogenesis of IBD, additional therapeutic peptides with innovative mechanisms of action are expected to emerge.

# 6. Delivery strategies of peptides

## 6.1. Administration method

Peptide administration for IBD can be achieved through various routes, including oral, rectal, and injectable delivery.[103] Among these, oral administration offers several advantages, such as non-invasiveness, ease of self-administration, flexible dosing, and elimination of sterile preparation requirements, making it particularly attractive for improving patient adherence and satisfaction.[104] However, this route presents significant challenges: the acidic environment of the GI tract can degrade peptides, and impaired intestinal absorption—particularly in IBD patients with compromised digestive function—further reduces bioavailability.[105] Moreover, a substantial proportion of orally administered drugs undergo first-pass metabolism, where absorption by intestinal enterocytes and subsequent hepatic processing significantly diminishes the bioavailability of peptide therapeutics.[106] As a result, higher doses are often required to achieve therapeutic efficacy, which may increase the risk of adverse effects.

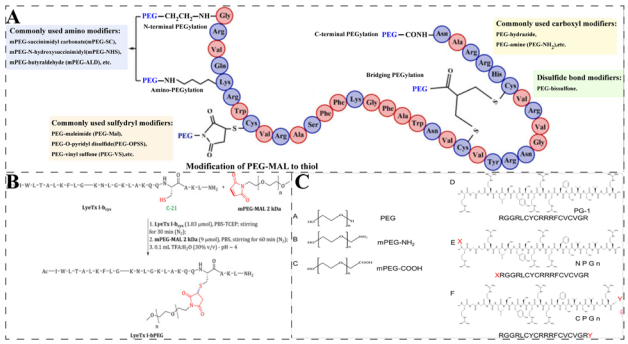



Fig. 7 (A) PEG-modified sites in peptides. Reproduced from ref. 112 with permission from Frontiers Media S. A., copyright 2024. (B) LyeTx I-b cys conjugation process to form LyeTx I-bPEG. Reproduced from ref. 113 with permission from Frontiers Media S. A., copyright 2022. (C) Molecular structure of PEG and its derivatives and different PEGylation sites of peptides. Reproduced from ref. 115, with permission from American Chemical Society, copyright 2021.

Systemic delivery methods, in contrast, bypass first-pass metabolism, enhancing bioavailability while reducing the required dosage and associated side effects.[107] This highlights a major limitation of oral peptide delivery for IBD treatment.

Rectal administration provides localized delivery of biologics, directly targeting intestinal inflammation. This approach circumvents both gastric degradation and hepatic metabolism, allowing rapid mucosal absorption and minimizing systemic exposure.[108] By enhancing therapeutic efficiency and potentially reducing treatment costs, rectal delivery is particularly promising for long-term disease management. Nevertheless, its effectiveness remains limited by the intestinal mucosa's low permeability, which restricts drug absorption and overall bioavailability.[102,109]

Injectable peptide delivery provides distinct clinical advantages. It enables localized sustained release, enhances bioavailability while minimizing systemic exposure, avoids GI degradation, facilitates gut microbiota-mediated immunomodulation, and promotes tissue regeneration when combined with bioactive scaffolds.[103] Clinical advances, particularly improved depot formulations, have extended peptide half-life and reduced the frequency of administration, contributing to better therapeutic outcomes.

Recent progress in biomaterials science has further revolutionized peptide delivery. Innovative platforms—including functional nanomaterials, hydrogels, and engineered probiotics—have been developed to enhance IBD therapy. These engineered carriers exhibit superior GI stability and targeted retention within the colon, overcoming the harsh intestinal environment. Their sophisticated design allows precise spatiotemporal control of peptide release while protecting therapeutic payloads from degradation, significantly improving mucosal targeting, drug stability, and therapeutic efficacy.

## 6.2. PEGylation of peptides

The majority of bioactive peptides exhibit limited aqueous solubility, insufficient structural stability, and rapid

degradation, posing significant challenges to their pharmacological performance and clinical application.[110] Chemical modifications, particularly PEGylation, have been widely employed to enhance the pharmaceutical properties of peptides, improving their solubility, structural stability, and overall therapeutic potential. PEGylation involves the covalent attachment of polyethylene glycol (PEG) chains to peptides, leveraging PEG's exceptional biocompatibility, hydrophilicity, and low immunogenicity.[111] Substantial progress has been made in the development of PEG-conjugated peptides, capitalizing on the flexible and desirable characteristics of PEG (Fig. 7A).[112] PEGylation can be performed at various sites, including the N-terminus, C-terminus, amino groups, sulfhydryl groups, and *via* bridging strategies.

Moreira Brito *et al.* investigated the structural and functional effects of PEGylation on the antimicrobial peptide LyeTx I-b, demonstrating that the PEGylated derivative, LyeTx I-bPEG, exhibited enhanced resistance to proteolytic enzymes such as trypsin while maintaining antimicrobial activity and reducing cytotoxicity (Fig. 7B).[113] These findings highlight its promising potential for biotechnological and therapeutic applications. Another study systematically evaluated the influence of PEG molecular weight, architecture, and conjugation chemistry on peptide delivery efficiency and cytotoxicity, revealing that these parameters critically affect the performance of PEGylated peptides.[114] Moreover, PEGylation has been shown to substantially improve the pharmacological properties of AMPs, notably by increasing their stability and protease resistance (Fig. 7C).[115] The researchers found that NPG and CPG exhibited greater stability against trypsin degradation and enhanced antibacterial activity.

In a related example, site-specific PEGylation at Lys30 was employed to modify porcine glucagon-like peptide-2 (pGLP-2).[116] The resulting mono-PEGylated conjugate demonstrated marked improvement in proteolytic stability and therapeutic efficacy. Notably, it resisted enzymatic degradation *in vivo* and significantly alleviated DSS-induced colitis in murine models. This strategy effectively addresses the pharmacokinetic limitations of pGLP-2 while preserving its biological activity, offering a blueprint for the broader application of PEGylation in enhancing the stability and efficacy of therapeutic peptides vulnerable to enzymatic degradation.

The biological activity and pharmacological properties of peptides are intricately linked to their chemical structures. A wide array of modification strategies—ranging from backbone engineering (*e.g.*, D-amino acid substitution, *N*-methylation, and peptoid incorporation) to side-chain analog replacement and peptide cyclization—have been developed to enhance proteolytic stability, improve binding affinity, and optimize membrane permeability.[117–120] Emerging techniques such as genetic code expansion further enable the introduction of non-canonical amino acids, significantly expanding the structural and functional diversity of peptide therapeutics.[121] These chemical modifications play a pivotal role in transforming native peptides into drug-like molecules with improved efficacy and stability, as comprehensively reviewed by Wang *et al.*[122]

### 6.3. NPs as a delivery strategy for peptides in IBD

NPs typically comprise three structural components: the surface, shell, and core. Due to their excellent biocompatibility, non-toxicity, and structural versatility, NPs have been widely applied in drug delivery systems.[6] Their intrinsic targeting capability enables the reduction of drug dosages, thereby minimizing systemic side effects. In the context of peptide delivery, NPs offer significant advantages, including protection against enzymatic degradation and enhanced mucosal penetration.

**6.3.1. Chitosan (CS).** CS, a linear polysaccharide derived from the deacetylation of chitin, possesses several advantageous properties such as low cost, renewable sourcing, and strong mucoadhesion.[123] In acidic environments, its amino groups become protonated, rendering CS the only naturally occurring cationic polysaccharide. It has been approved by the FDA for various applications, including dietary supplements, tissue engineering, and drug delivery.[124] As a nanomaterial, CS facilitates the reversible opening of intestinal epithelial tight junctions, enhancing both paracellular and transcellular transport. Furthermore, its abundant amino ($-NH_2$) and hydroxyl (–OH) groups allow for facile chemical modifications, enabling functional versatility.[125]

CS NPs (CS-NPs) have emerged as a promising platform for targeted colonic delivery of therapeutic peptides, largely due to their strong mucoadhesive interactions with the negatively charged mucin layer.[126] In a relevant study, Intiquilla *et al.* investigated the use of antioxidant peptides derived from *Lupinus mutabilis* seeds encapsulated within CS NPs for the targeted treatment of oxidative stress in IBD.[51] Two encapsulation methods—ionic gelation (CTPP-UF3) and spray freeze-drying (SFDC-UF3)—produced NPs with sizes of 332 nm and 465 nm, respectively, achieving high encapsulation efficiencies (63.80–71.75%) of the UF3 peptides while preserving antioxidant activity (>80%). Fourier-transform infrared (FT-IR) spectroscopy confirmed successful peptide-CS interactions, and both NP systems exhibited high biocompatibility (>70%

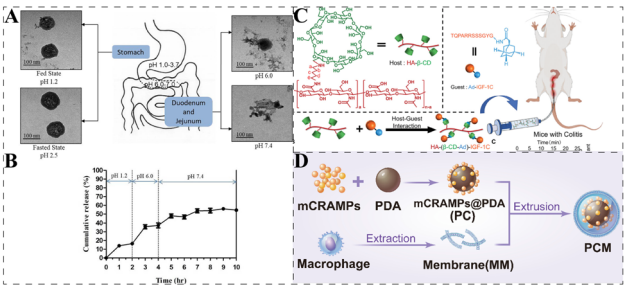



Fig. 8 (A and B) TEM images of SEMP-CS/F nanoparticles and their pH-dependent release behavior. Reproduced from ref. 127 with permission from Elsevier Ltd, copyright 2019. (C) Schematic of HA-β-CD supramolecular system for intrarectal delivery of IGF-1C. Reproduced from ref. 102 with permission from Wiley-VCH GmbH, copyright 2024. (D) Preparation of PDA nanoparticles encapsulated in macrophage membranes for mCRAMP delivery. Reproduced from ref. 49 with permission from Elsevier Ltd, copyright 2023.

viability in HT-29 colonic cells). However, the study lacked *in vivo* validation and long-term stability assessments, highlighting the need for further preclinical investigation before clinical application.

In another study, researchers developed soluble eggshell membrane protein-loaded CS/fucoidan NPs (SEMP-CS/F NPs) to promote intestinal epithelial repair (Fig. 8A and B).[127] The results demonstrated that SEMP-CS/F NPs significantly enhanced epithelial cell proliferation and barrier function, further validating the potential of CS-based NPs for the delivery of therapeutic peptides in GI disorders, including IBD.

**6.3.2. Hyaluronic acid (HA).** HA, a naturally abundant glycosaminoglycan, is widely distributed throughout extracellular matrices such as articular cartilage, dermal tissue, synovial fluid, and the ocular vitreous humor.[128] Its unique physicochemical characteristics confer exceptional biocompatibility, intrinsic anti-inflammatory properties, and favorable interactions with the gut microbiota.[129] Of particular therapeutic relevance, HA contributes to reinforcing mucosal barrier integrity, promoting epithelial wound healing, and mitigating pathological increases in intestinal permeability—critical factors in IBD management.[130]

As previously discussed in the mechanism section, Fu *et al.* developed a HA-β-cyclodextrin (HA-β-CD) supramolecular complex for the intrarectal delivery of the therapeutic peptide IGF-1C, combining sustained release capabilities with intrinsic anti-inflammatory effects (Fig. 8C).[102] Comprehensive characterization demonstrated enhanced stabilization of IGF-1C and sustained release kinetics, alongside potent anti-inflammatory and mucosal healing effects *in vivo*. Notably, 16S rRNA sequencing analysis revealed a significant increase in *Akkermansia* spp. abundance, suggesting that the HA-based system also modulated gut microbiota composition beneficially. In this platform, HA exhibited dual functionality by combining controlled IGF-1C delivery with intrinsic anti-inflammatory action.

In another recent study, Marotti *et al.* designed hybrid lipid-hyaluronate-KPV NPs loaded with teduglutide to stimulate endogenous glucagon-like peptide-2 (GLP-2) secretion.[131] The system, termed LNC-Ted HAKPV, offered three principal therapeutic benefits: (1) promotion of endogenous GLP-2 production to enhance intestinal growth and repair, (2) targeted anti-inflammatory action mediated through HA-KPV's modulation of the CD44/TLR4 pathways, and (3) redox-responsive release of the anti-inflammatory tripeptide KPV *via* disulfide bonds, activated under inflamed intestinal conditions. HA functioned not only as a delivery vehicle but also as an immunomodulatory agent, binding to CD44 receptors on immune cells such as macrophages, thereby suppressing their activation through TLR2/4 pathway modulation and reducing pro-inflammatory cytokine production. This multifunctional design highlights HA's versatility in both enhancing therapeutic efficacy and enabling targeted release within the inflammatory microenvironment characteristic of IBD.

**6.3.3. Polydopamine (PDA).** PDA is a versatile synthetic polymer known for its strong adhesive properties, enabling its use both as a surface coating for NPs and as an independent NP carrier.[132] PDA exhibits excellent biocompatibility, efficient cellular internalization across a wide range of cell types, and considerable chemical functionalization flexibility, making it highly suitable for drug delivery applications.[133] Beyond these physical attributes, PDA also possesses intrinsic anti-inflammatory properties—partly by inhibiting effector T-helper cell production—and demonstrates potent antioxidant activity due to the abundance of reductive groups within its molecular structure.[134,135]

Bao *et al.* explored the therapeutic potential of PDA NPs conjugated with an AMP and further coated with a macrophage membrane for targeted treatment of IBD *via* ROS scavenging and gut inflammation targeting (Fig. 8D).[49] They developed inflammation-targeting PDA NPs capable of modulating both gut immunity and microbiota, thereby presenting a dual-action therapeutic strategy. Their results showed that the PDA NPs effectively alleviated oxidative stress and restored gut microbiota balance, significantly relieving IBD symptoms. This study highlights PDA-based NPs as a promising platform for GI disorder therapies, with particular emphasis on ROS scavenging as a pivotal mechanism in IBD management.

**6.3.4. Poly(lactide-*co*-glycolide) (PLGA).** PLGA is an FDA-approved biodegradable polymer extensively utilized in drug delivery systems due to its ability to encapsulate both hydrophobic and hydrophilic therapeutics.[136] As a protective carrier, PLGA shields encapsulated drugs from enzymatic degradation while enhancing therapeutic efficacy through improved mucosal adhesion. This adhesive property further promotes the absorption of drugs and peptides, optimizing treatment outcomes.[137] Notably, PLGA degradation products, particularly lactate, can stimulate angiogenesis and accelerate wound closure. In one study, researchers successfully encapsulated LL37—an AMP—within PLGA NPs, creating a PLGA-LL37 NP system that significantly enhanced wound healing by combining sustained LL37 release with lactate-mediated biological activity.[138]

In another investigation, Yan *et al.* developed an innovative theranostic nano-platform for the diagnosis and treatment of

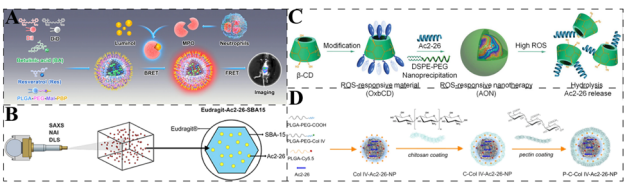



Fig. 9 (A) Preparation of PBP-PLGA nanoparticles encapsulating BA and Res, modified with PLGA-PEG-Mal and PBP and labeled with DiL and DiD. Reproduced from ref. 47 with permission from Springer Nature, copyright 2024. (B) Synthesis process of SBA-15-Ac2-26. Reproduced from ref. 48 with permission from Taylor & Francis Group, copyright 2024. (C) Development of ROS-responsive nanoparticles by chemically functionalizing β-cyclodextrin (β-CD) with OxbCD, linked to Ac2-26 and DSPE-PEG. Reproduced from ref. 144 with permission from Elsevier Ltd, copyright 2019. (D) Layer-by-layer chitosan nanoparticle system for protecting Ac2-26 from the harsh gastrointestinal environment. Reproduced from ref. 145 with permission from Springer Nature, copyright 2024.

UC (Fig. 9A).[47] They engineered PBP-decorated PLGA NPs (PBP-PLGA-NPs) co-loaded with two anti-inflammatory compounds—betulinic acid and resveratrol—along with lipophilic fluorescent dyes for imaging purposes. These NPs exhibited favorable physicochemical characteristics, including an average size of 164.18 nm and high drug entrapment efficiency (>50%). Leveraging PLGA's biodegradability, biocompatibility, and controlled release properties, this system effectively encapsulated therapeutic agents. Moreover, PBP surface modification enhanced targeting specificity, reduced immunogenicity, and prolonged sustained drug release *in vivo*, offering a promising strategy for integrated UC diagnosis and therapy.

**6.3.5. Lipid-based delivery systems.** Lipids, which can be derived from both natural and synthetic sources, represent a versatile platform for peptide delivery; however, precisely categorizing them as strictly natural or synthetic often remains challenging.[138] Lipid NPs offer significant promise for peptide therapeutics due to their diversity, excellent biocompatibility, and targeted functionality.[139] Common lipid components—such as glycerides, free fatty acids, fatty alcohols, and phospholipids—are frequently utilized owing to their favorable physicochemical properties, including natural surface activity, enhanced membrane permeability, and the ability to spontaneously form structured carriers through self-assembly.[140]

Sterically stabilized micelles (SSMs) constitute a robust class of self-assembled lipid nanocarriers, particularly suited for encapsulating and delivering amphiphilic peptides. Their nanostructure effectively protects peptides from proteolytic degradation, significantly extends systemic circulation time, and improves overall bioavailability.[141] Jayawardena *et al.* employed SSMs to deliver VIP, a neuropeptide with potent anti-inflammatory effects, for the treatment of IBD.[54] This lipid-based system notably enhanced the bioavailability and therapeutic efficacy of VIP.

Additionally, a newly developed lipid nanoemulsion (NE) system was designed to facilitate the delivery of poorly soluble active drugs.[142] By integrating NEs with self-assembling peptide hydrogels, this hybrid system improves the encapsulation efficiency of both NEs and drugs, supporting applications in IBD therapy. The platform achieves gastric retention, controlled intestinal release, and minimized systemic drug exposure. These advancements build upon prior studies discussing peptide delivery using lipid-based nanocarriers, as outlined in the existing literature.[139]

**6.3.6. Other NPs.** In addition to conventional NP systems, other nanocarriers such as silica mesoporous NPs, mesoporous carbon NPs (MCNs), and specially designed bioactive NPs have been investigated for peptide delivery in IBD therapy. Broering *et al.* developed an innovative approach using the Annexin A1 (AnxA1) mimetic peptide Ac2-26 encapsulated within SBA-15 mesoporous silica microparticles for oral delivery (Fig. 9B).[48] Their system (SBA-15-Ac2-26) achieved a high peptide loading efficiency (88%) and successfully delivered Ac2-26 into macrophages (Raw 264.7) and epithelial cells (Caco-2). Oral administration of Eudragit®-coated SBA-15-Ac2-26 effectively alleviated colitis symptoms and promoted epithelial repair in a murine IBD model. Although the low absorption of SBA-15 in non-inflamed gut tissues could limit its overall efficacy, the inflamed intestinal barrier enhanced particle uptake, supporting the potential of Ac2-26 as a minimally invasive and cost-effective IBD therapy.

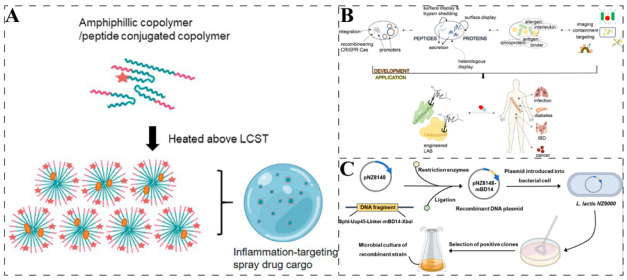



Fig. 10 (A) Formation of nanomicelles above LCST for drug loading. Reproduced from ref. 43 with permission from Elsevier Ltd, copyright 2022. (B) Development and medical application of engineered lactic acid bacteria (LAB). Reproduced from ref. 155 with permission from Springer Nature, copyright 2019. (C) Construction and therapeutic application of engineered *Lactococcus lactis* expressing mBD14. Reproduced from ref. 156 with permission from American Chemical Society, copyright 2023.

MCNs, carbon-based nanomaterials characterized by high biocompatibility, large surface area, and controllable mesoporosity, have also emerged as promising platforms for peptide delivery.[143] A mitochondria-targeting nanoplatform was recently developed by conjugating folic acid-modified MCNs with the bioactive peptide M27-39, achieving dual therapeutic effects against both colorectal cancer and IBD.[50]

Beyond material innovations, novel peptide-based nanotherapies have been designed to exploit pathological microenvironments for targeted release. Li *et al.* introduced oxidation-responsive NPs (AONs) loaded with the Ac2-26 peptide, which selectively release their payload in ROS-rich inflamed tissues (Fig. 9C).[144] These NPs modulated inflammatory pathways, enhanced neutrophil efferocytosis, and promoted anti-inflammatory macrophage phenotypes. Similarly, Lee *et al.* developed pectin-coated polymeric NPs (P-C-Col IV-Ac2-26-NPs) encapsulating Ac2-26 for oral delivery (Fig. 9D).[145] The pectin coating protected the NPs during gastric transit and enabled localized release in the colon *via* microbial pectinase degradation, while collagen IV targeting enhanced NP adhesion to injured colonic tissues. These advanced systems exemplify the evolving landscape of NP-enabled peptide delivery for IBD treatment.

### 6.4. Hydrogels applied in the delivery of peptides for IBD

Compared to NPs, hydrogels offer several distinct advantages, including superior biocompatibility, strong mucosal adhesion, environment-responsive release kinetics, versatile chemical tunability, customizable formulations, and sustained-release capabilities.[146–149] Hydrogels are primarily composed of polymers such as alginate, hyaluronic acid, and CS, typically formed through non-covalent interactions. Peptides, as chains of amino acids, can also form hydrogels, benefiting from inherent

biocompatibility, ease of modification, and the potential for specific functional design to meet therapeutic needs.[150]

A pioneering study by Yoon *et al.* introduced an innovative "all-in-one" therapeutic strategy for IBD by integrating diagnostic and therapeutic functions (Fig. 10A).[43] They developed an endoscopically applicable, sprayable nanomicelle hydrogel capable of lesion-targeted adhesion and drug-free treatment. Key methodological innovations included (1) peptide conjugation to modulate Toll-like receptor 5 (TLR5) and Notch-1 signaling pathways, mimicking interactions with *Bacillus subtilis* flagellin, and (2) comprehensive validation across multiple models, including cell lines, patient-derived cells, organ-on-chip systems, murine models, and porcine studies. The hydrogel demonstrated dual functionality, enabling real-time endoscopic visualization while suppressing inflammatory responses through TLR5/Notch-1 crosstalk without relying on conventional pharmacological agents. This study marks a significant advancement in targeted IBD therapy using multifunctional hydrogel systems.

The integration of NPs with hydrogels further enhances therapeutic potential by enabling specific functionalization and sustained release, leveraging the hydrogel's versatile encapsulation capabilities. For instance, Andretto *et al.* developed a hybrid lipid-polymer system by combining mucopenetrating nanoemulsions with a bioadhesive peptide-based hydrogel, PuraStat.[142] PuraStat, composed of self-assembling RADA16 peptide sequences, exhibits excellent structural integrity under physiological conditions and possesses inherent anti-inflammatory properties. This nanosystem, featuring oral bioavailability, sustained release, and targeted delivery, synergistically combines the advantages of its individual components. The platform demonstrated improved therapeutic efficacy for IBD, underscoring its potential as a targeted and effective treatment strategy.

### 6.5. Engineering bacteria for peptide delivery in IBD

LAB represents a heterogeneous group of Gram-positive microorganisms widely utilized in the food industry. Recognized by the FDA as safe for human consumption, many LAB strains possess the ability to withstand the harsh conditions of the GI tract and successfully colonize it, making them promising candidates for enhancing intestinal health.[151,152] However, the properties of wild-type LAB are often uncontrollable and may not achieve the desired therapeutic outcomes. Recent advances in bacterial engineering now enable the intelligent design of LAB with tailored functions, including targeted drug and peptide delivery capabilities.[153]

A recent review provided a comprehensive overview of bacterial modification strategies and evaluated their potential applications in treating IBD.[154] Researchers have proposed engineering bacteria to deliver therapeutic molecules or perform diagnostic functions in the gut by leveraging synthetic biology techniques. Similarly, Plavec and Berlec explored the potential of genetically engineered LAB as delivery systems for therapeutic proteins and peptides (Fig. 10B).[155] Their study highlighted diverse genetic engineering strategies, including surface display systems and secretion mechanisms, to enhance targeted delivery. These approaches have shown promise in facilitating the effective administration of cytokines, vaccines, and other bioactive molecules through both oral and mucosal routes.

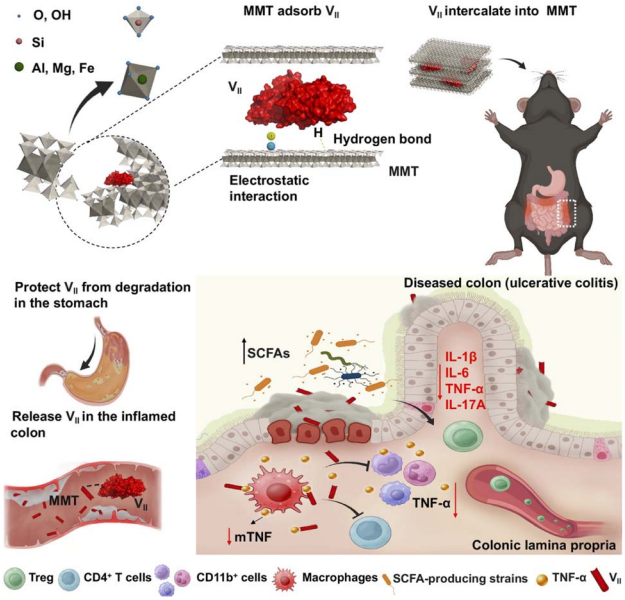



Fig. 11 The MMT-based adjuvant system protects anti-TNF-α nanobodies from gastrointestinal degradation while exerting anti-inflammatory effects and modulating gut microbiota. Reproduced from ref. 164 with permission from National Academy of Sciences, copyright 2024.

In a related study, Tian *et al.* investigated the therapeutic potential of *Lactococcus lactis* NZ9000 engineered to express mouse β-defensin 14 (mBD14) for IBD treatment (Fig. 10C).[156] β-Defensins, as AMPs, possess notable anti-inflammatory properties; however, their clinical application has been limited by high production costs, low yields, and sensitivity to degradation within the GI tract. To address these challenges, the researchers developed *L. lactis* NZ9000/mBD14 through a three-step process: synthesizing and cloning the Usp45-Linker-mBD14 fusion gene into the pNZ8148 plasmid, electroporating the recombinant plasmid into competent *L. lactis* NZ9000 cells prepared using a sucrose/glycerol/EDTA method, and verifying mBD14 expression in both the culture supernatant and cell lysate *via* western blot analysis. This engineered probiotic system enables cost-effective and stable delivery of mBD14 to the gut, establishing a promising foundation for developing novel IBD therapies. These findings provide a theoretical basis for further exploration of *L. lactis*/mBD14 as a potential therapeutic approach for IBD.

### 6.6. Montmorillonite (MMT)–Related peptide delivery

Montmorillonite (MMT) is a widely studied mineral clay characterized by its large surface area, strong adsorption capacity, and ion-exchange properties. This biocompatible material demonstrates excellent GI tolerance and has been effectively

utilized to adsorb pathogenic bacteria and toxins, exhibiting both antidiarrheal and antibacterial therapeutic effects.[157]

MMT exhibits minimal systemic absorption due to its inability to permeate the GI epithelium, ensuring its elimination alongside adsorbed toxins without interfering with normal bowel function.[158] Moreover, the net negative surface charge of MMT promotes selective accumulation at sites of inflammation within the intestinal lumen through electrostatic interactions with positively charged proteins abundant in inflamed tissues.[159] This targeted localization, combined with its high adsorption capacity, positions MMT as an effective platform for site-specific peptide delivery in IBD.

Significant efforts have been made to utilize MMT for drug and peptide delivery. For instance, Jing and colleagues successfully incorporated dihydromyricetin (DHM) into the interlayer galleries of MMT through a solution-based intercalation approach, followed by solvent removal *via* rotary evaporation. The resulting hybrid material demonstrated therapeutic efficacy in a murine model of UC, underscoring its potential for managing intestinal inflammation.[160]

Recent research has also shown that PDA-modified MMT (PDA-MMT) exhibits potent ROS-scavenging properties and selectively accumulates in inflamed intestinal regions.[161] Upon reaching the colon, this nanocomposite forms an adherent protective layer over ulcerated mucosa, effectively reducing inflammatory responses and promoting epithelial regeneration. These combined effects accelerate mucosal healing in experimental models of IBD.[162]

In a related approach, MMT was modified with copper ions to further enhance its therapeutic efficacy for IBD treatment. Additionally, researchers developed a novel nanoformulation integrating MMT, diallyl trisulfide (DATS), and peptide dendrimer nanogels (PDNs). In this system, DATS enabled controlled and sustained $H_2S$ release, offering antioxidant and anti-inflammatory effects.[163] Although PDNs alone underwent rapid degradation in the GI tract, encapsulation with MMT effectively compensated for this limitation, leading to significant therapeutic benefits in IBD models.

Furthermore, a recent study by Huang *et al.* demonstrated that MMT could serve as a multifunctional adjuvant, protecting anti-TNF-α nanobodies (VHH) from GI degradation while modulating gut microbiota (Fig. 11).[164] The interlayer spaces of MMT stabilized VHH *via* electrostatic and hydrogen-bonding interactions involving carboxylate and amino groups, facilitating targeted intestinal release for enhanced IBD treatment. Collectively, these findings highlight the promising role of MMT as a multifunctional platform for peptide and protein delivery in IBD therapy.

Besides the aforementioned delivery strategies, several other methods have also been developed to improve the stability and bioavailability of peptide therapeutics. Emulsion-based delivery systems, such as oil-in-water (O/W) and water-in-oil (W/O) emulsions, are particularly useful for hydrophilic peptides that require protection from aqueous environments.[165] These emulsions create compartments that shield peptides from enzymatic degradation and facilitate controlled release.

Albumin, a well-established circulatory protein, has also been widely explored as a carrier in advanced drug delivery systems, including those for peptides.[166] For example, Gao *et al.* developed a composite nanoparticle system based on bovine serum albumin and chitosan to enhance peptide delivery efficiency and biocompatibility.[167] Peptide–protein conjugation represents another versatile approach for improving delivery performance. Yurkevicz *et al.* designed a tumor-targeting delivery system utilizing a pH (low) insertion peptide (pHLIP) as a platform to deliver the immunogenic SIINFEKL peptide to the tumor microenvironment.[168] This strategy exploits the acidic pH of the tumor milieu to enable selective insertion and delivery, thereby enhancing targeting precision.

Collectively, these alternative delivery strategies expand the toolbox for peptide formulation, offering tailored solutions to overcome challenges such as poor stability, enzymatic degradation, and limited tissue targeting—thereby advancing the clinical potential of peptide-based therapeutics.

## 7. Conclusion and perspectives

In this review, we briefly summarized the pathophysiology of IBD and current clinical management strategies. We also examined therapeutic peptides—including their sources, structures, and mechanisms of action in IBD treatment—and discussed recent advances in peptide delivery technologies. Although the pathophysiology of IBD remains incompletely understood, it is evident that novel therapeutic strategies are urgently needed for its effective management.

Therapeutic peptides offer a safe and efficient alternative to traditional drugs, with the potential to minimize side effects commonly associated with conventional therapies. Advances in computing power, data availability, and algorithms have enabled deep learning (DL) to transform peptide research. Successes in peptide synthesis and bioactivity prediction underscore its potential, while the growing integration of AI into pharmaceutical workflows reflects the accelerating adoption of these technologies. As demand for novel peptide therapeutics rises, breakthroughs such as large-scale peptide libraries for clinical trials show promise in treating conditions like cancer and diabetes. Moreover, progress in novel biomaterials, formulations, and delivery strategies continues to enhance the precision, stability, and targeted delivery of peptide-based therapies, further advancing their clinical applications. To accelerate drug design and clinical translation, integrating big data and DL is essential. Constructing benchmark datasets and incorporating structural or evolutionary data can improve model reliability and predictive power.[169] Additionally, refining sequence representations offers opportunities for developing peptide-specific models, enhancing clinical relevance. In the future, DL and computational advances will continue to propel peptide discovery, with the synergy between biology, data science, and clinical application unlocking the full potential of peptide therapeutics.

However, several key challenges must be addressed to facilitate the successful development and clinical translation of new peptides and delivery platforms:

(1) Peptide sequence analysis and mechanistic exploration

A comprehensive analysis of therapeutic peptide sequences is crucial to elucidate their exact mechanisms of action in IBD treatment. Deepening our understanding at the molecular level will not only optimize therapeutic efficacy but also inspire the development of innovative delivery systems and next-generation peptide drugs.

(2) Ensuring peptide safety

Although bioactive peptides are generally regarded as safe, many naturally occurring peptides possess toxic or allergenic properties.[170] Therefore, rigorous evaluation of newly synthesized peptide sequences and structures is essential to ensure safety before clinical application.

(3) Optimizing dosage and long-term application

Determining the optimal dosage is critical, as inappropriate peptide concentrations—like conventional drugs—may induce adverse effects.[171] Furthermore, given the chronic and recurrent nature of IBD, long-term studies are required to assess the safety and therapeutic durability of peptide-based treatments.

(4) Assessing novel delivery systems

Despite the rapid development of advanced delivery technologies, most novel systems remain in preclinical stages. Successful clinical translation demands a thorough evaluation of biosafety, alongside a detailed investigation of absorption, distribution, metabolism, and excretion (ADME) properties.[172]

(5) Improving preclinical models

Existing chemically induced IBD models have notable limitations and do not fully replicate human disease mechanisms. The development of more physiologically relevant and diverse preclinical models is essential to better evaluate and predict the performance of biomaterial-based peptide delivery systems.

In summary, the combination of therapeutic peptides with advanced delivery strategies offers immense promise for enhancing biological therapies in IBD treatment. While significant challenges remain, peptide-based therapeutics are emerging as a transformative platform, heralding a new era of targeted, safer, and more effective interventions in IBD management and precision medicine.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

## Author contributions

Conceptualization, C. G.; resources, Y. W.; visualization, C. G.; writing – original draft, Z. W.; writing – review & editing, C. G. and M. W. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

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