



Strategies and opportunities of micro/nano delivery systems for targeted therapy of ulcerative colitis: Focus on underlying mechanisms and future perspectives

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ABSTRACT

Ulcerative colitis (UC) is a common progressive inflammatory disease whose incidence has increased rapidly in recent years, and can develop into colorectal cancer in severe cases. There are currently no adequate or effective treatments for UC due to the fact that some patients have found suboptimal results after repeated administration, while others have experienced adverse effects. With the rapid development of nanotechnology, developing innovative colon-targeting platforms is essential to improving efficacy, reducing side effects, and improving patient compliance. In this review, we summarize the pathophysiological characteristics of UC and the most recent status of numerous nanodrug delivery systems based on different targeting mechanisms in treating UC. Oral, intravenous, and rectal drug delivery nanoparticles targeting the colon are discussed, which can provide ideas for the design of colon-targeting nanoparticles for the treatment of colon diseases, especially for the treatment of UC. Last but not least, we provide a glimpse into the future of colon-targeted delivery systems, as well as future advancements in the field.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic and prone to relapse immune-mediated disease with a multifactorial pathogenesis, including Crohn's disease (CD) and ulcerative colitis (UC) [1,2]. The prevalence of IBD in many countries in North America, Oceania, and Europe exceeds 0.3% [3], and is increasing rapidly even in regions with a low prevalence, such as Southern and Eastern Europe, Asia, and most developing countries [4]. Over the past 40 years, some Asian countries have seen an increase of 1.5-fold to nearly 20-fold in the incidence and prevalence of UC [5].

Similar to CD, UC is a progressive disease rather than a superficial disease confined to the rectal and colonic mucosa [6,7]. Disease progression is accompanied by many adverse consequences such as proximal extension of the disease, strictures, colorectal dysfunction, impaired colonic permeability, and reduced responsiveness to drug therapy, and may also lead to submucosal fibro-

sis, increased risk of cardiovascular disease associated with the chronic nature of UC [6,8], and even effects on brain and cognitive functions [9]. Additionally, patients with UC are at a higher risk of developing colorectal cancer, which may be associated with the dysregulation of immune cells and cytokines, as well as intestinal inflammation due to the dysregulation of intestinal ecology [10–12]. Reactive oxygen species (ROS) produced by inflammatory infiltration can cause abnormal proliferative lesions, and the risk of progressive transformation of UC into colitis-associated colorectal cancer increases as the lesions become more extensive and prolonged [13,14]. Timely and accurate diagnosis holds paramount importance in guiding appropriate therapeutic interventions, disease monitoring, and prognosis prediction for UC patients. Currently, the diagnosis of UC is based on a combination of clinical symptoms, endoscopic evaluation, and histological analysis [2,15]. Nanoparticles have applications in UC-related biomarker detection [16,17], imaging diagnostics, and colonic tissue histopathological examination. In this context, researchers employ nanoparticles, such as magnetic nanoparticles, as imaging enhancers by integrating them with imaging probes [18]. Leveraging the nanoparticle accumulation characteristics within inflamed colonic regions,

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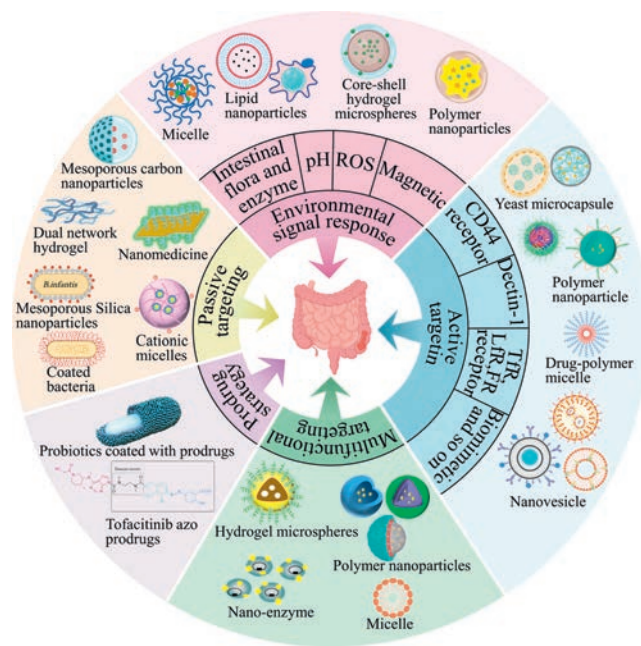
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this approach enhances the sensitivity and specificity of techniques like magnetic resonance imaging (MRI) and nuclear magnetic resonance fluorescence imaging (NIRF) [19–22]. Consequently, high-resolution imaging of UC inflammatory zones is achieved, assisting clinicians in accurately diagnosing the location and extent of UC lesions. Furthermore, nanotechnology offers novel prospects for the development of integrated diagnostics and therapeutics [23,24], facilitating early detection, personalized treatment, and continuous monitoring to achieve disease control and long-term remission.

The etiology of UC is complex and not fully understood. Environmental factors (such as smoking, dietary habits, and antibiotic use), genetic factors, microbiota imbalance, immune dysfunction, excess ROS, reactive nitrogen species (RNS), and pro-inflammatory cytokines including tumor necrosis factor (TNF)- α and interleukin (IL)-6 are all closely related to UC occurrence and development [25–29]. In patients with UC, multiple pathways may be activated, and there may be changes in pathways during progression as a result of environmental exposure, epigenomic, proteomic, and metabolomic changes, as well as abnormalities in structural organization [7].

Both pharmacological and surgical treatments are available for UC. The treatment method for patients depends mainly on the severity of the disease, degree of inflammation, and its evolutionary stage over time. Most patients with UC receive pharmacological treatment, and those with refractory UC, poor tolerance, and UC-related neoplastic changes undergo surgical treatment, which greatly reduces their quality of life, leading to disability and psychological stress [30–32]. Current pharmacological treatments for UC can be divided into conventional therapies, biological therapies, and novel targeted small molecules. Conventional therapies include oral or topical rectal application of 5-aminosalicylic acid (5-ASA) and its derivatives, corticosteroids, thiopurine immunomodulators, and oral or intravenous glucocorticoids such as prednisolone [33–35]. Biological therapies include three available biological agents, namely the TNF- α antagonists infliximab, adalimumab, and golimumab; the anti- $\alpha 4\beta 7$ integrin vedolizumab; and the IL-12/IL-23p40 antagonist ustekinumab [36–40]. Novel targeted small molecules include Janus kinase (JAK) inhibitors such as tofacitinib [41–45]. Owing to an improved understanding of the etiology and pathogenesis of UC, new drugs, including the JAK inhibitor upadacitinib, S1P receptor agonist ozanimod, anti-integrin antibody etrolizumab, and natural alkaloids, are also being explored [46–50]. Additionally, therapies targeting the microbiota, such as fecal microbiota transplantation, antibiotics, probiotic and microbial metabolite inhibitors, and phage therapies, are under development [51–55]. For example, some investigators have administered colonoscopic infusion, enema, or oral lyophilized fecal microbial transplantation capsules to replenish a patient's disrupted intestinal ecosystem with microorganisms harvested from healthy donors to control UC progression [56–60].

Although several treatment options are currently available, these therapies require frequent administration to patients and are associated with high relapse rates, severe adverse effects, increased drug resistance, non-response to drugs, and high prices of antibody drugs, and their therapeutic efficacy is still far from optimal [7,61–66]. Therefore, there is an urgent need for well-designed and versatile delivery systems for the targeted therapy of UC to develop more effective treatments and achieve specific release of active substances at the site of intestinal inflammation, maximize efficacy, minimize systemic side effects, reduce the frequency of administration, and improve patient compliance, thereby overcoming the limitations of current UC treatment. With the development of nanotechnology, many colon-targeting nanodrug-delivery systems for UC therapy have emerged [67], such as liposomes, microparticles, and polymeric nanoparticles, which facilitate the delivery of small molecule compounds, peptides and proteins, nucleic acids



Scheme 1. Colon-targeted delivery systems based on different mechanisms for ulcerative colitis treatment.

(especially siRNA), and vaccines (Scheme 1). Based on the great advantages of nano-delivery system in passive targeting and active targeting, nano-delivery vehicles show broad application prospects in the diagnosis and treatment of diseases [68–71].

2. Physiological and pathological microenvironment characteristics of UC

From the stomach to the intestine, enzymatic activity, pH, motility, and fluid content change considerably, and each organ exhibits different characteristics [72,73]. Compared to the stomach and small intestine, the colon has fewer and less active enzymes, lower levels of digestive enzymes and bile salts, less penetration resistance, milder pH conditions (6–8), lower activity intensity and fluid volume, and longer drug retention time (up to 20 h) [72,74,75]. Therefore, the colon is an ideal site for large- and small-molecule drug delivery, which improves the bioavailability of poorly absorbed and acid- or enzymatically degradable drugs. Additionally, the colon is abundant in lymphoid tissue, which absorbs antigens into the mast cells of the colonic mucosa, thereby enabling the rapid production of local antibodies that contribute to effective vaccination [76].

The microenvironment surrounding the colonic site in patients with UC has unique characteristics (Fig. 1), such as the epithelial enhanced permeation and retention (EPR) effect, formation of a positively charged environment, reduced pH, elevated levels of ROS and multiple inflammatory factors, high expression of certain enzymes and receptors, and microbial imbalance. These features form the basis for the design of colon-targeting nanodrug delivery systems (NDDS).

Similar to tumor tissue, the UC inflammatory mucosa has defective enterocyte membranes exhibiting loss of tight junctions and cellular integrity, which result in the loss of barrier function in inflammatory regions, migration of inflammatory cells, and increased permeability to nanodrugs, a phenomenon known as the EPR effect [77,78]. Nanoparticles less than 200 nm in diameter can penetrate deeper into the intestinal mucus layer of patients with UC via the EPR effect [79,80]. The inflammatory site has a positively charged environment, which is associated with the *in situ* accumu-

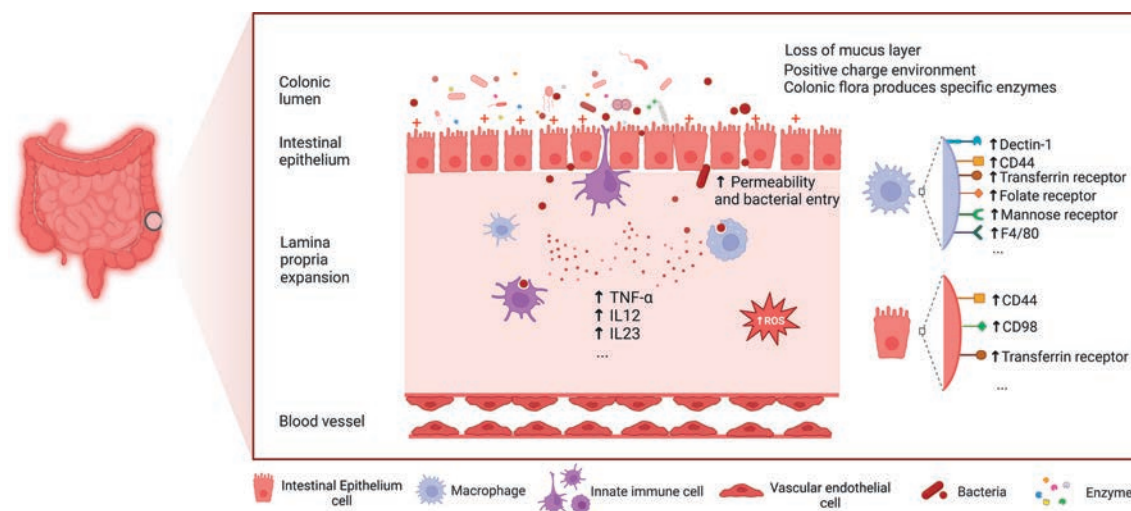


Fig. 1. Characteristics of pathological microenvironment of UC.

lation of positively charged proteins, including transferrin, ferritin, eosinophilic cationic proteins, and bactericidal or permeability-enhancing proteins [81] (in contrast, mucins secreted by damaged intestinal epithelial cells have a negative charge [82]). This characteristic allows negatively charged nanoparticles to easily accumulate in damaged areas (including epithelial cells and macrophages). Compared with healthy intestinal tissue, the pH of the colonic region is significantly lower in patients with UC [74,83] and can even be reduced to approximately 3.0 [84]. Patients with UC have abnormal immune regulation; the microenvironment around the disease site has higher ROS levels, and an imbalance in important antioxidants can trigger oxidative stress and lead to mucosal damage [14,85,86]. The immune dysfunctional response also leads to overexpression of several inflammatory factors [87]. Furthermore, certain enzymes are overexpressed in the microenvironment, such as α -amylase, neutrophil elastase, and myeloperoxidase [88]. Additionally, the expression of four members of the JAK family, such as tyrosine kinase 2, JAK1, JAK2, and JAK3, is upregulated in active UC. JAK3 is upregulated in a subpopulation of inflammatory fibroblasts, whereas it is absent in healthy intestinal mucosa [42]. Moreover, the high expression of certain receptors or cell adhesion molecules on colonic epithelial cells or macrophages during disease progression provides potential binding sites for active targeting of drug delivery [89–91]. Finally, the intestinal flora of patients with IBD is characterized by a reduction in the abundance of bacteria belonging to the phyla Firmicutes (such as Ruminococcaceae and Lachnospiraceae [92,93]) and Bacteroidetes (such as enterotoxin-producing *Bacteroides fragilis* [94]), and an increase in the abundance of bacteria belonging to Actinobacteria and Proteobacteria (such as *Escherichia coli* [95] and the oral-associated pathogen *Klebsiella* spp. [96] and *Enterobacter* spp. [97]). Among them, the Lachnospiraceae family, belonging to the thick-walled phyla Clostridium cluster IV and XIVa, was significantly less abundant in IBD patients than in healthy population [98].

To achieve successful colonic targeting, the physiological properties of the colon and the differences between the inflamed gut and healthy peri-intestinal microenvironment must be considered when designing a colon-targeted drug delivery system, considering disease-induced changes in retention time, pH, microbiome, mucus composition, and permeability. Colon-targeted drug delivery systems should protect the drug from absorption in the upper gastrointestinal tract, degradation under acidic gastric conditions, and breakdown by proteases in the stomach and intestinal lumen and/or peptidases associated

with mucus and the intestinal mucosal brush border; and ultimately release upon reaching specific inflammatory sites in the colon [76,99], thus reducing systemic side effects and improving efficacy.

The main routes of administration for UC therapy are oral, intravenous, and rectal. Rectal administration is the fastest method of colon-targeted drug treatment for localized colon diseases, because higher doses can be delivered directly to the lesion, thus avoiding the pharmacokinetic problems associated with gastrointestinal motility, pH changes, and hepatic first-pass effects associated with oral administration [83,100,101]. Additionally, systemic exposure is much lower with rectal administration than with oral and intravenous administration, which greatly reduces the potential for side effects. For example, transrectal administration alleviates some of the adverse effects of glucocorticoids [102,103]. However, rectal administration cannot easily reach the proximal part of the colon, and self-administration is difficult for patients, which may cause discomfort and poor compliance [104]. Moreover, although effective, the clinical use of injectable drugs has been hampered by the general requirements of the procedure and specific injection techniques [105]. Oral dosage forms have non-sterile production requirements and low production costs, are easily handled by patients, and are characterized by accurate dosing and good stability and storage, and oral targeted delivery systems can increase intratumoral drug concentrations, reduce side effects, and improve treatment effect. Therefore, the oral route is generally considered the most desirable and acceptable route for UC treatment. Premature drug release or degradation can affect the treatment efficacy or even produce systemic side effects. Therefore, it is crucial to design reliable delivery systems to protect the drug from the devastating conditions of the stomach and intestine and to release the drug in a targeted and sensitive manner at the site of colitis.

3. Micro/nano-drug delivery systems targeting UC

In recent decades, various NDDS have been developed for UC treatment based on the pathophysiological characteristics of the colonic site. These include prodrug strategies, passive targeting strategies based on electrostatic interactions and EPR effects, ligand/receptor-mediated active targeting-dependent strategies, inflammatory targeting [106], and environmental signal response strategies (including pH response, ROS response, gut microbiota and enzyme response, and magnetic response).

3.1. Prodrug strategy

Prodrug strategies are often used to mitigate the side effects of drugs, maintain probiotic activity, and enhance colonization at the colonic site, and are effective options for colonic targeting [107]. Ideally, a colon-specific prodrug should be both stable and not be absorbed by the upper gastrointestinal tract, but rather be released and absorbed completely in the colon [108]. In this study, we reviewed pharmacologically active molecules linked to materials, such as glycosides, amino acids, cyclodextrins, pectins, and glucuronides, to form adducts that can be digested by specific enzymes generated by the intestinal flora developed for colon-specific drug delivery [109,110]. Among these, azo adducts hold great promise.

Tofacitinib has a substantial effect in patients who do not respond adequately to conventional therapy; however, its systemic adverse effects prevent its use at high doses. Zhao *et al.* [87] synthesized an azoic precursor to tofacitinib that was similar to basalazide by first constructing an azoic bond between *p*-aminobenzyl alcohol (PABA) and 5-ASA, and then linking tofacitinib with 5-ASA-PABA using two efficient self-immolating linkers, methylene alkoxy carbamate and diamine, to obtain a new azoic

precursor. The drug is released by the cleavage of the azo bond in the presence of azo reductase produced by the intestinal flora. This system successfully achieved colonic targeting of tofacitinib *in vivo*. Additionally, a mouse model of oxazolone-induced colitis showed that the dosage of the azo prodrug was significantly lower than that of tofacitinib and did not damage natural killer cells while achieving the same efficacy, and that tofacitinib dose-related systemic adverse effects could be avoided (Fig. 2A).

The azoic prodrug basalazide has also been used to construct probiotic coatings. In another study, Zhang *et al.* [111] conjugated basalazide with 1-palmitoyl-*sn*-glycero-3-phosphocholine to form a lipid precursor coating, which was modified by interfacial supramolecular self-assembly on the surface of *Lactobacillus rhamnosus* GG (LGG) to construct engineered probiotic bacteria (LBL). After oral administration, this lipid pre-drug coating can not only resist gastric and intestinal digestive juices and maintain the biological activity of probiotics but also enter the colon to release 5-ASA, inhibit colonic inflammation, improve the pathological environment, and provide a microenvironment conducive for LGG colonization. LGG effectively colonized the intestine and subsequently regulated the intestinal flora to synergistically improve UC pathology (Fig. 2B).

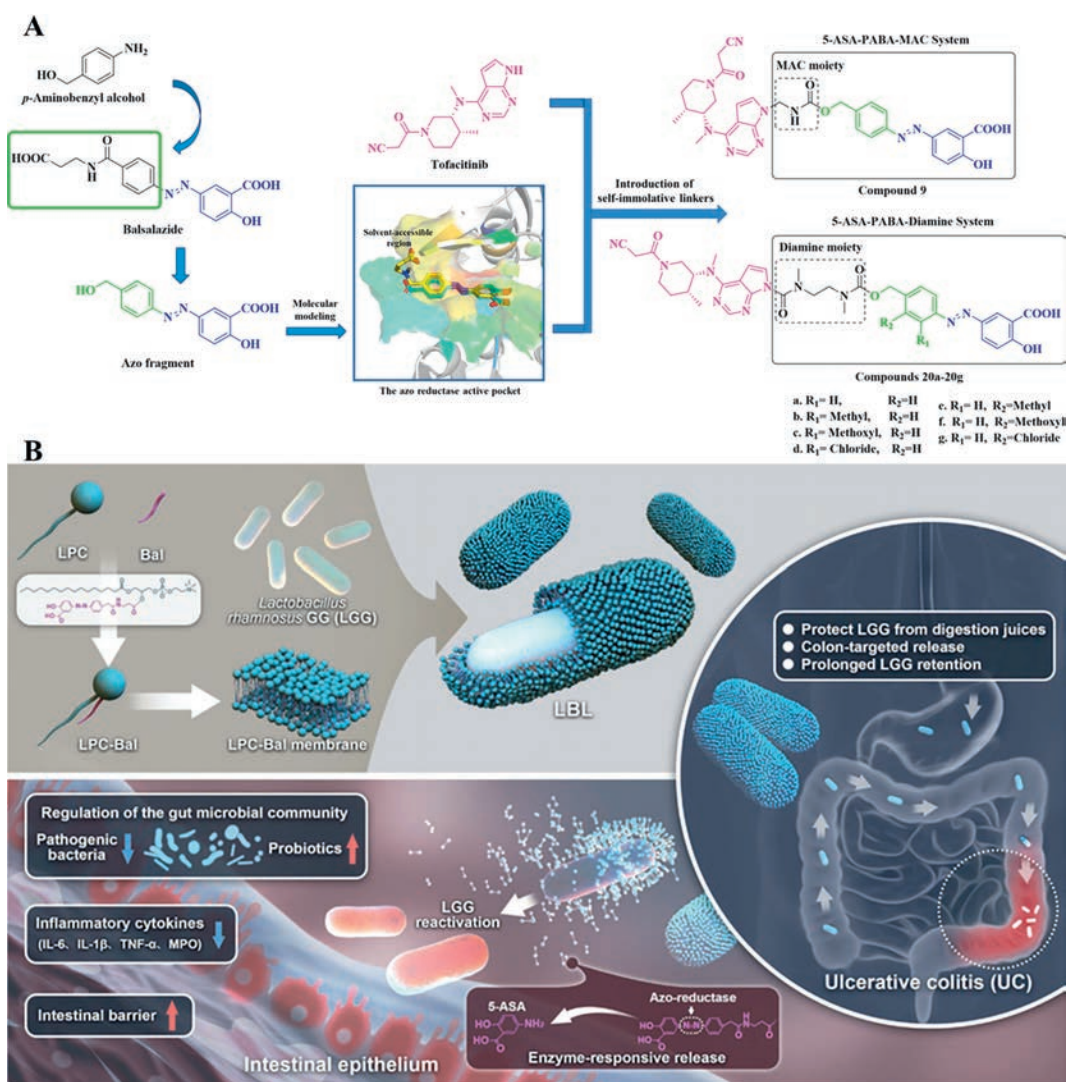


Fig. 2. (A) Design strategy of colon-targeted azo prodrugs of tofacitinib. Copied with permission [87]. Copyright 2022, American Chemical Society. (B) The LBL preparation process and the mechanism of LBL treatment of UC. Copied with permission [111]. Copyright 2022, Wiley-VCH GmbH.

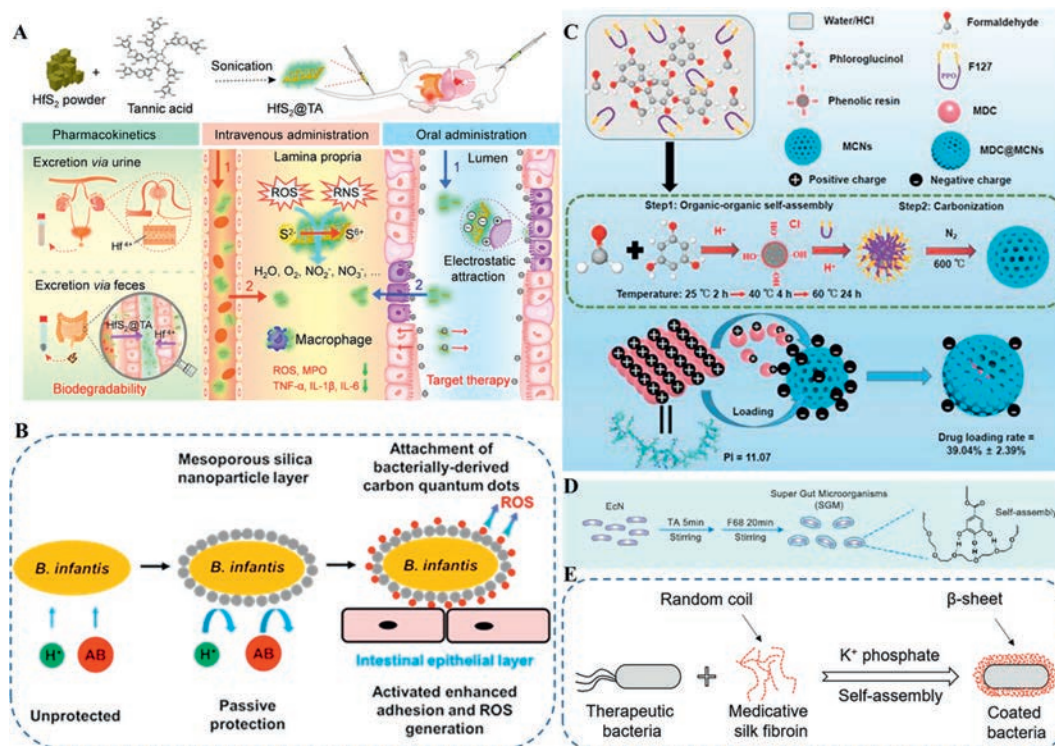


Fig. 3. (A) Illustration of the exfoliation process for targeted treatment of IBD via oral or intravenous administration of HfS₂@TA atomic crystals. Copied with permission [26]. Copyright 2022, American Chemical Society. (B) An illustration of how bacteria are encapsulated in a shell of mesoporous silica nanoparticles, followed by their activation by bacterially-derived CQDs. Copied with permission [114]. Copyright 2022, Elsevier Ltd. (C) The construction of a MDC-loaded nano-platform using MCNs (MDC@MCNs) as well as the synthesis procedure and schematic illustration of the shape evolution path of MCNs. Copied with permission [112]. Copyright 2021, Ivyspring International Publisher. (D) Schematic diagram of the preparation of Super Gut Microorganism (SGM). Copied with permission [115]. Copyright 2022, Elsevier B.V. (E) Using biointerfacial self-assembly to coat therapeutic bacteria with medicative silk fibroin. Copied with permission [116]. Copyright 2021, Wiley-VCH GmbH.

3.2. Passive targeting nanoparticles

The inflamed gut exhibits an eEPR effect and a positively charged mucosal surface, providing a molecular target for negatively charged delivery systems with small particle sizes. Table S1 (Supporting information) summarizes delivery systems based on the passive targeting principle. Zhang *et al.* [112] synthesized mesoporous carbon nanoparticles (MCNs) with small particle sizes and large pore sizes using a simple, effective, and optimized one-step soft template method under acidic conditions and prepared MDC@MCNs by loading *Musca domestica* cecropin (a novel peptide containing 40 amino acids) into MCNs using the principles of adsorption and charge interactions (Fig. 3C). MCNs exhibit enhanced adhesion to the diseased colon, facilitating subsequent transepithelial absorption. MDC@MCNs effectively alleviated dextran sodium sulfate (DSS)-induced UC by inhibiting inflammation and oxidative stress, ameliorating colonic epithelial cell injury, enhancing colonic tight junctions, and regulating intestinal flora. Zhao *et al.* [113] constructed a negatively charged rectally delivered dual network hydrogel system for the treatment of UC, which encapsulates the cationic model drug Lys-Pro-Val (KPV), a tripeptide derived from the C-terminal sequence of α -melanocyte-stimulating hormone. The hydrogel system is pH-dependent, erosive, highly conducive to long-term retention in the inflamed colon after intracolonic administration, and capable of achieving slow release of KPV over 24 h in a pH 5.5 medium.

Passive targeting-based nanomedicines have also been developed for UC treatment. Li *et al.* [26] developed a two-dimensional high-performance anti-inflammatory nanomedicine, tannic acid (TA)-coated hafnium disulfide ultrathin HfS₂@TA nanosheets, with desirable ROS scavenging and targeting abilities using a liquid-

phase exfoliation method. Owing to the electrostatic interaction between the negatively charged tannic acid and the positively charged inflammatory epithelial cells, HfS₂@TA maintained a good targeting ability to the inflamed colon, even in a harsh gastrointestinal environment. Owing to the S²⁻/S⁶⁺ valence shift and large specific surface area, HfS₂@TA nanosheets achieved good therapeutic effects in both the DSS-induced UC model and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced CD model after oral or intravenous administration, not only effectively eliminating ROS/RNS and downregulating pro-inflammatory factors but also excreting them through the renal and hepatic-intestinal systems. Hafnium-based nanomaterials are also expected to be useful for targeted diagnosis of IBD (Fig. 3A).

Probiotics can improve the intestinal mucosal barrier and immune system function by reducing the levels of the pro-inflammatory factors TNF- α and IL-1 β and increasing the levels of the anti-inflammatory factor IL-10 through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and nuclear factor kappa B (NF- κ B) signaling pathways, thereby inhibiting the growth of harmful intestinal bacteria, and have been used to improve UC symptoms [117]. For example, Wei *et al.* [114] developed a hybrid probiotic in which *Bifidobacterium infantis* was wrapped in a boron hydroxyl-modified active mesoporous silica nanoparticle layer, and then used click chemistry to attach carbon quantum dots (CQDs) from *Lactobacillus acidophilus* or *E. coli* to the layer to form *B. infantis*@SiO₂@L-CQDs and *B. infantis*@SiO₂@E-CQDs systems, respectively. The attachment of CQDs enhanced adhesion properties and activated a passive protective shell by enhancing ROS production (Fig. 3B). In other studies, negatively charged therapeutic nanocoatings of tannic acid@Poloxamer 188 (TA@F68) (Fig. 3D) [115] or silk fibroin (Fig. 3E) [116] or were used to encapsulate

E. coli Nissle 1917. These coatings increased the adhesion and colonization capacity of probiotic bacteria without destroying their activity.

Researchers have developed positively charged delivery systems to achieve colonic targeting by interacting with negatively charged mucins secreted by damaged intestinal epithelial cells. Liu *et al.* [118] formed micelles with hydrotic quinoa protein (HQP), an amphiphilic peptide, to co-encapsulate hydrophobic quercetin (Que) and epigallocatechin 3-gallate (EGCG), both of which have synergistic effects in the treatment of UC. The delivery system Que-HQP-EGCG with a negatively charged core and modified cationic coupling starch (CLRS) as the encapsulated shell formed the delivery system, Que-HQP-EGCG-CLRS composite micelles. These micelles with a core-shell structure facilitated the stable passage of both drugs through the gastric environment, effective accumulation in the inflammatory zone of the colon, and sustained drug release for more than 24 h, resulting in substantial relief of UC symptoms.

3.3. Environmental signal-responsive nanoparticles

In light of the specific pathological microenvironment associated with UC, diverse environmental signal-responsive delivery systems have been devised. These encompass pH-responsive, ROS-responsive [119,120], intestinal flora and enzyme-responsive, as well as magnetic-responsive systems [121]. Natural and synthetic polymers and their derivatives are commonly used as carriers [122,123]. Natural polysaccharides are widely used as an ideal colonic targeting material due to their easy accessibility, low cost, high bioavailability and biocompatibility, pH and ROS responsiveness, gastric resistance, bioadhesion, degradability of colonic microbiota and ease of modification [75,124,125]. Polysaccharide polymeric materials, such as gum [126,127], chitosan (CS) [128–130], alginate [131,132], inulin [133–135], cyclodextrin [119,136], guar gum [137,138], starch [139–141], are used as a matrix or part of the coating of different delivery systems, such as micro/nano systems and hydrogels to load therapeutic/diagnostic reagents, or are modified into various types of polymeric nanoparticles, lipid-polymer complexes, and liposomes for colonic targeting [142].

3.3.1. Intestinal flora decomposition and enzyme degradation

Numerous colonic flora produce enzymes such as α -amylase, β -glucosidase, β -galactosidase, β -xylosidase, cellulase, deaminase, azo reductase [143], nitro reductase, and cyclodextrinase. Moreover, a multitude of polymeric materials, such as pectin, CS and its derivatives, dextrose, starch, and sodium alginate, exhibit resistance to degradation in the gastric and intestinal milieu, yet can be selectively degraded by specific enzymes secreted by colonic flora [144]. CS, a naturally-occurring polycationic amino polysaccharide, possesses inherent structural modifiability, making it amenable to alterations. Its distinctive features, including colony- and enzyme-specific degradation, along with adhesive properties, offer promising prospects for effective colon-targeted delivery in the realm of scientific literature. For instance, Cao *et al.* [145] used CS as a hydrogel matrix co-transplanted with immobilized insulin-like growth factor-1 C-structural domain peptide and human placenta-derived mesenchymal stem cells, and after injection into the margins of injured colonic mesentery, the system improved colitis in mice via phenyl glycidyl ether 2 (PGE₂)-mediated polarization of M2 macrophages (Fig. 4C). Additionally, CS has been used as a surface coating to modify materials [144] such as esterase-responsive lipid and poly(lactic-co-glycolic acid) (PLGA) nanoparticles [146]. CS is frequently utilized for the purpose of establishing complexes with a variety of synthetic or natural polymers, including sodium alginate [147] and natural proteins [148]. This strategic utilization aims to augment the efficacy of drug delivery to the colon while concurrently enhancing drug stability within the gastrointestinal tract.

In a recent study by Deng *et al.* [149], a novel strategy was developed for the oral administration of exosomes. The researchers employed a layer-by-layer self-assembly technique using two polysaccharide derivatives, namely *N*-(2-hydroxy)propyl-3-trimethylammonium CS and oxidized konjac glucomannan, which can be degraded by β -mannanase, to encapsulate mesenchymal stem cell (MSC)-derived exosomes (MSC-Exos) (Fig. 4B). Furthermore, Liu *et al.* [132] constructed adhesive hydrogel cores (formed by cross-linking antimicrobial silver ions with thiolated-hyaluronic acid (HASH), a thiosemicarbazone with anti-inflammatory proper-

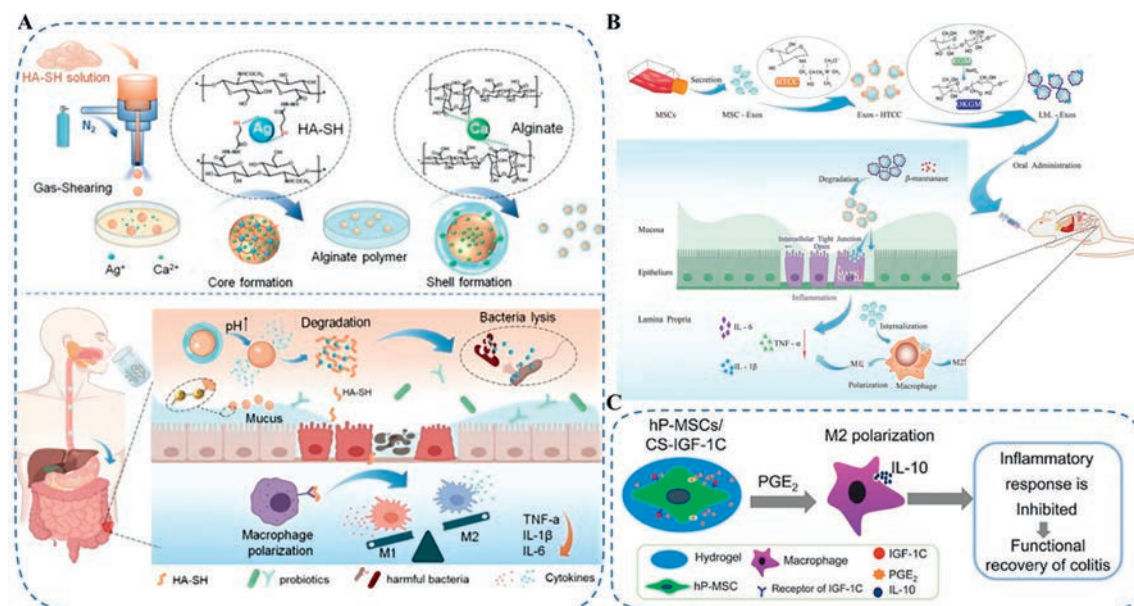


Fig. 4. (A) Core-shell hydrogel microspheres for colon-targeted treatment of UC. Copied with permission [132]. Copyright 2021, Wiley-VCH GmbH. (B) A schematic illustration highlights the preparation and mechanism of action associated with colon-targeted layer-by-layer exosomes (LbL-Exos), enhancing UC treatment. Copied with permission [149]. Copyright 2023, Elsevier B.V. (C) A diagram outlines the therapeutic effects of human placenta-derived mesenchymal stem cell (hP-MSCs) and chitosan (CS)-based injectable hydrogel with immobilized IGF-1 C domain peptide (CS-IGF-1C) hydrogel cotransplantation for colitis treatment. Copied with permission [145]. Copyright 2020, Ilyspring International Publisher.

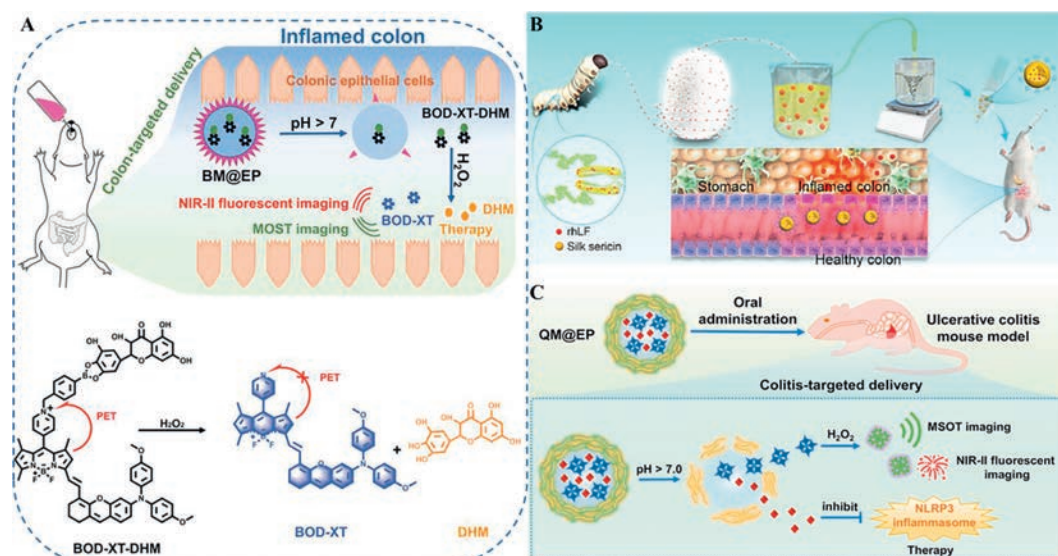


Fig. 5. (A) BM@EP nanosystem enables targeted delivery of chromophore-drug dyad (BOD-XT-DHM) to the colon, triggered by colonic pH and activated by overexpressed H_2O_2 in inflamed colon, facilitating colitis therapy and diagnosis via optoacoustic/near-infrared second window (NIR-II) fluorescent imaging. Copied with permission [154]. Copyright 2022, Wiley-VCH GmbH. (B) Silk sericin nanospheres (SS-NS-rhLF), derived from silkworm middle silk gland, exhibit negative charge ($\text{pH} \geq 5$) and specifically accumulate at colitis sites. Released rhLF from SS-NS-rhLF is internalized by colitis tissue macrophages, suppressing inflammatory factor production and effectively treating UC. Copied with permission [153]. Copyright 2022, Elsevier Ltd. (C) QM@EP nanosystem, administered orally, showcases the versatile actions of activatable probe QY-SN- H_2O_2 and resultant AIEgen QY-SN-OH upon encountering H_2O_2 . Copied with permission [155]. Copyright 2022, Elsevier Ltd.

ties) using advanced gas shearing techniques and then prepared calcium alginate hydrogel shells with acid resistance, high degradability, and colon-targeting properties via ion diffusion (Fig. 4A). Colon-targeted adhesion of core-shell hydrogel microspheres was designed and prepared. The two-step preparation process was efficient and precise, and provided a versatile platform for oral drug delivery.

Other researchers have proposed novel starch-based nanocarrier designs. Xu *et al.* [88] synthesized curcumin (CUR)-hydroxyethyl starch couples via ester bonds and self-assembled them to form polymeric micelles. Recently, Song *et al.* [150] synthesized tryptophan metabolite indole-3-acetic acid-esterified high straight-chain maize starch (HAMS) using resistant starch as carrier HAMS. HAMS resists catabolism and absorption in the small intestine, facilitating its fermentation by intestinal microbiota. This microbial fermentation produces short-chain fatty acids, crucial for promoting intestinal homeostasis and maintaining gastrointestinal equilibrium. The detailed characteristics of these delivery systems can be found in Table S2 (Supporting information).

3.3.2. pH response

Natural pH differences exist between different organs of the gastrointestinal system. An ideal pH-responsive system needs to have high sensitivity and a narrow pH response range to prevent degradation damage caused by disturbances from healthy sites, especially gastric acid, to achieve precise drug release at the colonic site [85]. pH-stimulated responsive polymers are widely used owing to their customizable design, structural flexibility, and cost-effectiveness. Specifically, anionic polymers, which exhibit insolubility at low pH levels, but undergo structural changes and drug release in the higher pH environment (6–8) of the intestinal tract, preventing degradation in the stomach and enabling colonic delivery and high bioavailability of weakly alkaline drugs [151]. These delivery systems are important for achieving oral drug delivery for the treatment of UC (Table S3 in Supporting information).

Commonly employed polymers for colon-targeted delivery include poly(methacrylic acid-methyl methacrylate) copolymers (such as Eudragit L, S, and F), hydroxypropyl methylcellu-

lose (HPMC) 50 and 55, hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and shellac [151,152]. Another researcher [153] developed a genetically engineered silk fiber using silk fibroin and sericin as the main components. A pH-responsive system of recombinant human lactoferrin (LF) in silk gum nanospheres was prepared using an ethanol-precipitation method. In a $\text{pH} \geq 5.5$ environment, the negatively charged filamentous proteins achieved specific targeting to positively charged colonic sites. Eudragit S100 (ES) dissolved above pH 7.0 and exerted local specificity and immediate drug release in an oral colonic targeting delivery system (Fig. 5B). Zhang *et al.* [84] employed two pH-sensitive materials, Eudragit EPO (soluble at pH below 5.0) and Eudragit L100 (soluble at pH above 6.0), as coating agents for nanosized CUR to form programmed pH-responsive nanoparticles with a core-shell structure. After oral administration, CUR was released into an acidic microenvironment (pH 3.0) at the ulcer site but not throughout the colon. This significantly increased the concentration of CUR in the inflammatory zone, thereby improving drug efficacy and alleviating UC symptoms in mice.

The combination of polymers with different properties forms a multifunctional system with simultaneous pH- and ROS-responsiveness [156–158], controlled-release [159,160], time-dependence, microbial, and enzyme responses [80,138,161], and mitochondrial targeting [162]. Oshi *et al.* [163] effectively addressed the problem of uncontrolled initial drug release from alginate particles in the stomach and small intestine by enteric-coating them with ES and CS, enabling targeted delivery of cyclosporine A (CsA) crystals to the colon.

Some investigators have used pathological colonic H_2O_2 -responsive chemical bonds to bind drugs and chromophores to form dichromats (Fig. 5A) [154], or fluorescent probes containing chemical groups that can be cleaved by H_2O_2 co-encapsulated with drugs [155] and then enteric-coated with ES and PLGA, with extended-release properties for UC imaging, detection, and therapy (Fig. 5C). The utilization of different ratios of Eudragit polymers presents a suitable approach for the design and development of pH-dependent oral colon-targeted drug delivery systems, as sub-

stantiated in the existing body of scientific literature. For example, Sardou *et al.* [142] used a 3^2 full factorial design to predict an optimal coating comprising a time-dependent water-insoluble polymer (Eudragit RS) and two enterosoluble materials, Eudragit S (soluble at pH 7) and Eudragit L (soluble at pH 6), for colon-specific delivery of 5-ASA particles. The findings from this investigation revealed that an optimized S, L, and RS ratio of 16:64:20 w/w, along with a coating level of 15%, demonstrated superior efficacy in facilitating the targeted delivery of 5-ASA particles to the colon.

3.4. Active targeting nanoparticles

Colonic epithelial cells and macrophages play a pivotal role in the inflammatory cascade of colitis, making them highly desirable target cells for therapeutic intervention [164]. In IBD, the upregulation of receptors and cell adhesion molecules on colonic epithelial cells and immune cells [165], such as folate receptor [166], transferrin receptor [167], lactoferrin receptor, CD44, CD98 [168], peptide transporter 1 (PepT1), mannose receptor [169,170], and Dectin-1, enables the design of targeted nanoparticles for effective therapy. The characteristics of these nanoparticles are listed in Table S4 (Supporting information).

3.4.1. Targeting the CD44 receptor

CD44 exhibits substantial surface expression on colonic epithelial cells and macrophages within colitis tissues, rendering it a promising and effective therapeutic target for UC intervention [165]. The natural polysaccharides hyaluronic acid (HA) and chondroitin sulfate specifically bind to and are internalized by activated macrophages *via* the highly expressed CD44 receptor. Among them,

HA, a biocompatible and biodegradable polysaccharide with a negative charge and immunomodulatory properties, is a commonly used carrier material.

For instance, Chen *et al.* [171] superimposed negative HA on the surface of positively charged TB (formed by the self-assembly of two herbal compounds, TA and berberine, *via* hydrogen bonding and other forces) to achieve colon-targeted delivery through HA-CD44 interactions (Fig. 6C). In additional investigations, bilirubin (BR), recognized for its robust antioxidant properties, has been chemically conjugated with HA to form HA-BR. Through self-assembly, HA-BR serves as a nanomedicine platform, giving rise to the development of HABN nanoparticles [172]. BR demonstrates remarkable ability in scavenging ROS and provides protection to HA from degradation and inactivation mediated by hyaluronidase, even in challenging oxidative environments. The results showed that HABN could target the colonic epithelium, restore the epithelial barrier, maintain intestinal flora homeostasis, modulate the innate immune response, and exert a strong therapeutic effect on colitis (Fig. 6A). IL-10 is a cytokine with anti-inflammatory properties involved in the maintenance of the intestinal immunity [173]. In another study, HA-BR was modified on a vector surface to achieve IL-10 mRNA activity and accurate targeted delivery [174]. Briefly, IL-10 mRNA binds to the polyphenol ellagic acid *via* supramolecular binding to produce negatively charged nuclear mRNA/E, which is then complexed with linear polyetherimide (PEI) to obtain positively charged mRNA/EP, which is then coated with BR-modified HA to obtain mRNA/EPHB (Fig. 6B). The binding of polyphenols to nucleic acids effectively reduces the risk of enzymatic cleavage by nucleic acids. After transrectal administration, the nanostructure specifically upregulated IL-10 levels, effectively inhibited

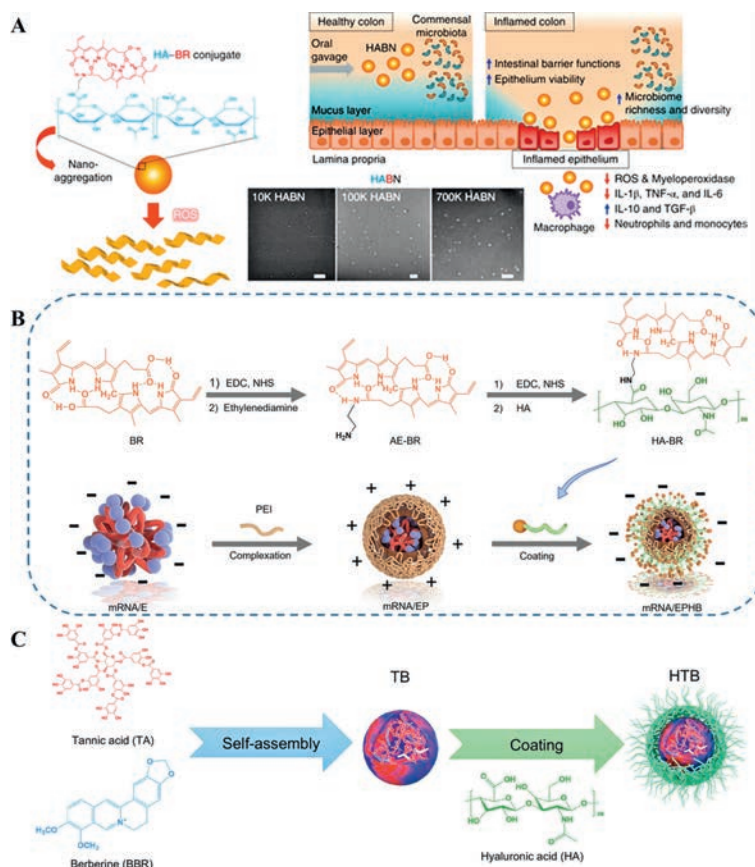


Fig. 6. (A) Schematic and TEM images depict the self-assembly of HABN nanoparticles derived from HA-BR. Copied with permission [172]. Copyright 2019, Springer Nature. (B) Flowchart of chemical synthesis of HA-BR. Copied with permission [174]. Copyright 2022, Elsevier B.V. (C) Schematic diagram of preparing HTB. Copied with permission [171]. Copyright 2022, Elsevier B.V.

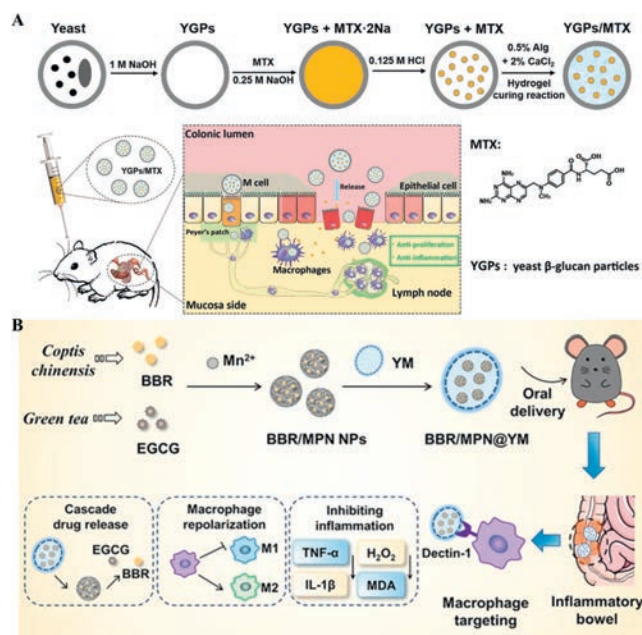


Fig. 7. (A) YGPs/MTX nanoparticles are prepared and specifically delivered to inflammatory sites, effectively suppressing intestinal inflammation when administered orally. Copied with permission [184]. Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) BBR/MPN@YM nanoparticles enable targeted treatment of UC by orally delivering Chinese herbal active ingredients to Peyer's patches, engaging the anti-inflammatory mechanism of mucosal immunity. Copied with permission [182]. Copyright 2022, American Chemical Society.

the expression of inflammatory factors, promoted mucosal repair, and protected colonic epithelial cells from apoptosis, which had a better therapeutic effect in DSS-induced acute and chronic colitis mouse models.

3.4.2. Targeting the dectin-1 receptor

Macrophages are the most abundant mononuclear phagocytes in the intestinal lamina propria and are essential for local homeostasis and maintenance of homeostasis between the commensal flora and the host. Dectin-1, a murine type II C-type lectin-like receptor, is the major β -glucan receptor on macrophages, and is capable of non-sonic recognition of β -1,3 and β -1,6-linked dextran-rich granules (such as mushroom polysaccharides [175]) and intact yeast [176,177]. Dectin-1 on macrophages mediates the recruitment of classical monocytes in intestinal inflammation, participates in the differentiation of macrophages towards an inflammatory phenotype and also regulates inflammasome-dependent IL-1 β secretion through the control of LTB₄ production [178]. Dectin-1 is highly expressed on colonic macrophages in patients with UC. In previous studies, yeast cell wall microcapsules (YM; also known as yeast dextran particles) prepared from yeast cells have been used as novel oral drug delivery vehicles for the treatment of various diseases such as diabetes, cancer, and cardiovascular diseases [179–181]. YM have a hollow porous structure with a pore size of approximately 2–5 μ m, are ellipsoidal in shape, and the main component is β -1,3-D glucan, which can effectively target the dectin-1 receptor of macrophages [182]. Additionally, YM has major advantages in facilitating lymphatic transport [183]. In oral delivery systems, YM protects the encapsulated drug from degradation in the acidic environment of the stomach and is broken down by β -glucanase, a metabolite of the intestinal flora, upon reaching the colonic site, thus facilitating the slow release of the drug. Currently, YM, when used as a drug delivery vehicle for UC therapy, has achieved encapsulation of the chemical drug methotrexate (Fig. 7A) [184] and the natural compound CUR [185], as well as

co-encapsulation of two natural compounds, berberine and EGCG, with synergistic effects (Fig. 7B) [182].

YM can also be loaded with drug nanoparticles with different functions, resulting in a multitargeted, multifunctional delivery system. For example, by encapsulating HA-modified nanoparticles (rhodopsin rhubarb acid (RH)-ovalbumin-polyethyleneimine (PEI)) into YM, these NPs can target CD44 receptors overexpressed by macrophages and epithelial cells, thus enhancing their inflammatory site-targeting ability upon release from YM. Similarly, other investigators have used LF, which targets intestinal epithelial cells, to encapsulate rhodopsin, which was then loaded into the YM to form a delivery system with two targeting layers: internal and external. These dual-targeting strategies improve the cellular uptake and enhance the anti-inflammatory and mucosal repair functions of drugs.

Zhang *et al.* [186] asymmetrically immobilized glucose oxidase and catalase on the YM surface and designed an adaptive dual bioengine yeast micro/nanorobot that can navigate autonomously through enzyme-macrophage switching to cross multiple biological barriers and accurately deliver drugs to the site of inflammation. Briefly, at homogeneous glucose concentrations, the surface enzymes of this system initiate glucose breakdown, leading to the formation of a localized glucose gradient, leading to the formation of a localized glucose gradient. This gradient drives the movement towards the gradient, enabling penetration of the intestinal mucus barrier through microfolded cellular transcytosis across the intestinal epithelial barrier. YM specifically targets and efficiently enters macrophages in Peyer's patches, autonomously migrating to inflammatory sites in the gastrointestinal tract. This allows for effective drug delivery into the circulatory system via intestinal administration.

3.4.3. Lipid-based biomimetic delivery systems

In addition to ligand-receptor binding strategies, nanoparticles can be actively targeted for inflammatory colonization using bionanotechnology. Macrophage membranes [119,187,188], engineered cell membranes [189], leukocyte membranes [190], and other biomimetic cell membranes have been used for active targeting of UC, and the detailed characteristics of these delivery systems are shown in Table S5 (Supporting information).

In a study conducted by Ma *et al.* [187], an intelligent bionic pH-responsive metal-organic framework (MOF) carrier [191], CCZM, by encapsulating carbon dot nanoparticles and CD98 clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) plasmid within zeolitic imidazolate framework-8 (ZIF-8) nanoparticles. The carrier was then camouflaged with macrophage membranes using a one-pot method. The bionic system demonstrated its ability to respond to pH, evade the immune system, and specifically target inflammation. After intravenous administration, the delivery system targeted the site of inflammation in UC by locating damaged blood vessels. In acidic environments (pH < 7), such as the inflamed region, the ZIF-8 enclosure was disrupted, leading to the release of nanoenzymes and plasmids. The released nanoenzymes effectively eliminated ROS and remodeled the inflammatory microenvironment. The CD98 CRISPR/Cas9 plasmid reduced CD98 expression at the genomic level, thereby alleviating inflammation (Fig. 8A). Wang *et al.* [189] transfected a CXCR4 recombinant lentivirus into MC-3T3 cells to obtain CXCR4-rich membranous MC-3T3 cell-derived cell membrane vesicles (CXCR4-CMVVs). Subsequently, CUR was wrapped in the engineered cell membrane capsule to form CXCR4/Cur-CMVVs. CXCR4/Cur-CMVVs have natural membrane surface properties, induce enhanced polarization of M2 macrophages, exhibit anti-inflammatory effects, and achieve colonic targeting through CXCR4-CXCL12 specific interactions.

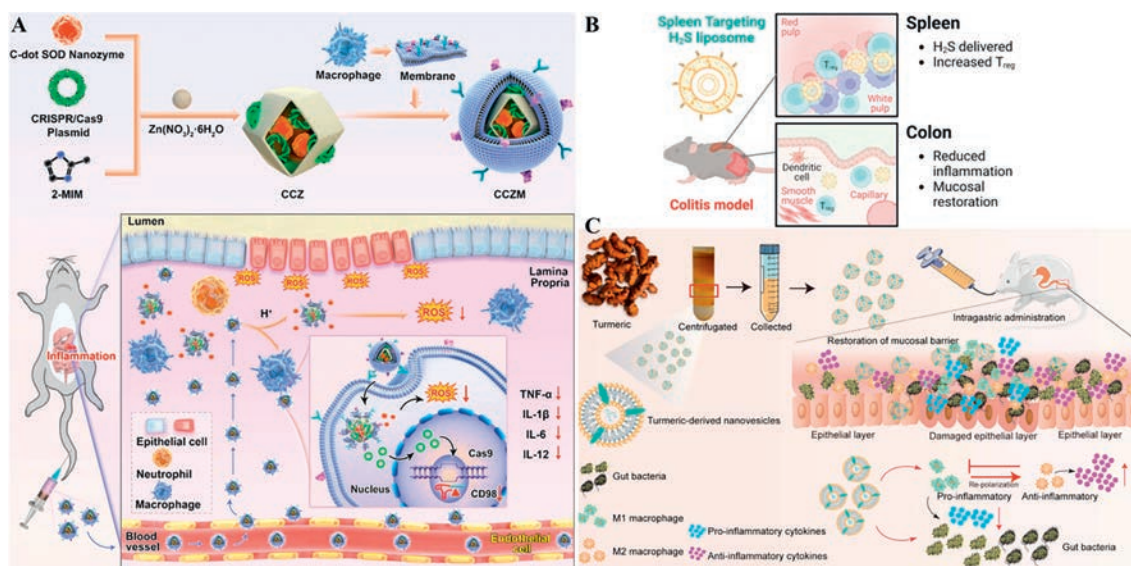


Fig. 8. (A) Synthesis and application of biomimetic MOFs. Copied with permission [187]. Copyright 2022, American Chemical Society. (B) Schematic illustration of the H₂S lipo treatment in DSS induced colitis model. Copied with permission [192]. Copyright 2023, American Chemical Society. (C) Schematic illustration of TNV preparation and anticolic efficacy. Copied with permission [193]. Copyright 2022, Ivyspring International Publisher.

Extracellular vesicles are particles that are naturally released from cells and comprise specific functionally active biomolecules such as bioactive lipids, proteins, or mRNAs [194,195]. As drug carriers, nanoscale extracellular vesicles or their analogs have unique structural and physicochemical properties, with the advantages of enhanced biocompatibility, low toxicity, intrinsic targeting (depending on their lipid composition and protein content [196]), ability to cross biological barriers, high internalization levels, and long circulating half-lives. Almost all cell types are capable of releasing vesicles into their extracellular environment [197]. Rao *et al.* found that co-incubation of dendritic cell (DC)-derived exosomes with tretinoin (TP) enabled selective entry of TP into DCs *in vivo*, thereby reducing their multi-organ toxicity [198]. Certain plant-derived exosomes have similar or even better therapeutic effects than those derived from the original plant. Ginger exosomes containing pharmacologically active ginger compounds (such as CUR and gingerol) have been shown to improve colitis and colitis-associated colorectal cancer in established animal models [199]. Turmeric-derived nanovesicles have also been shown to treat UC by restoring the damaged intestinal epithelial barrier, modulating the composition and relative structure of the intestinal immune microenvironment, remodeling the intestinal flora abundance, and remodeling the macrophage phenotype (promoting the conversion of the M1 phenotype to M2) (Fig. 8C) [193]. Other researchers have proposed new nanocarrier designs, such as ginger-derived recombinant liposomes [200], reverse-engineered liposomes [105], application of biosynthetic strategies [201], extracellular matrix-liposome composites [202], and lipid-polymer hybrid nanoparticles [203,204], which provide ideas for the development of lipid-based delivery systems.

In particular, Oh *et al.* [192] developed a long-circulating liposome loaded with an H₂S donor that exhibited high stability, high loading efficiency, and the ability to target the largest lymphoid organ, the spleen, to exert systemic immunomodulatory effects, showing great therapeutic potential in a model of DSS-induced colitis (Fig. 8B).

3.5. Multifunctional targeted nanoparticles

It is challenging to significantly alleviate inflammation, modulate immunity, and fully restore intestinal homeostasis based on

only one targeting mechanism. Therefore, it is necessary to combine multiple targeting mechanisms to enhance targeting ability. The design of drug delivery systems on the basis of multiple environmental signaling responses has been described previously. This section focuses on delivery systems designed by combining ligand-receptor interactions with other targeting mechanisms (Table S6 in Supporting information). Lee *et al.* [205] explored the potential of pH-sensitive ES-coated folate-grafted amino clay systems for the colon-targeted delivery of orally administered therapeutic antibodies. Some investigators have used negatively charged systems based on the unique physicochemical properties of inflammatory sites to achieve aggressive UC targeting (Fig. 9B). Gao *et al.* [85] combined the positively charged cerium oxide nanoenzyme CeO₂ with negatively charged HA and serotonin (5-HT) to obtain negatively charged HA-5-HT@CeO₂, thus achieving a dual mechanism of electrostatic attraction and HA-CD44 to target colonic inflammation. Similarly, nanocarriers prepared from the biopolymer composite HA-PLGA-chitosan showed good therapeutic potential as a strong anionic inflammatory targeting system loaded with the immunosuppressant CsA (Fig. 9A) [206]. Additionally, Miao *et al.* [169] designed and prepared a mannose-modified micellar delivery system loaded with quantum dots (QDs) and emodin by layer-coating with ES and CS as excipients, which achieved sensitivity to pH, colonic enzymes, and macrophages. Real-time tracking of QDs enables effective monitoring of carrier transport behavior *in vivo*, reveals the site of colonic ulcers, and achieves the design goal of combining UC diagnosis and treatment.

To further improve the targeting of the delivery systems, an increasing number of researchers have designed dual-targeting nanoparticles. Ye *et al.* [207] designed kelp polysaccharide (LA)-encapsulated, folate (FA)-modified LF nanoparticles encapsulated with CUR. LA is highly stable at extreme acidic pH and can be specifically degraded in the presence of β -glucanase. In the presence of dual-targeting LF and FA, nanoparticles target LF receptors on intestinal epithelial cells and FA receptors on macrophages and significantly reduce the symptoms of colitis after oral administration. Another study produced calcium pectinate and HA-modified LF nanoparticles encapsulated with RH, which protected the drug from the damaging effects of the gastrointestinal environment and delivered it to the colonic lesion [91].

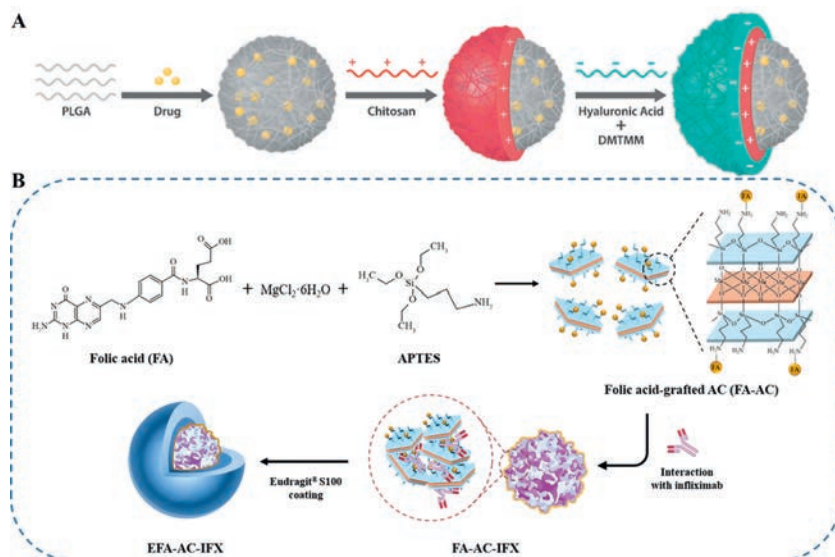


Fig. 9. (A) Schematic representation of CsA/ITNCs design and preparation. Copied with permission [206]. Copyright 2022, Elsevier Ltd. (B) A pH-responsive hybrid nanocomposite system for site-responsive oral delivery. Copied with permission [205]. Copyright 2022, Elsevier B.V.

4. Summary and prospects

In this review, we summarize and classify colon-targeted micro/nano delivery systems for UC therapy from the perspectives of targeting mechanisms and carrier material characteristics, encompassing prodrug strategies, passive targeting, pH and ROS responsiveness, gut microbiota modulation, ligand-receptor binding, and biomimetic nanoparticles. Designed for oral, intravenous, or rectal administration, these platforms offer promising avenues for achieving colonic targeting and enhancing therapeutic efficacy in UC treatment. In the process of colonic-targeted therapy, the utilization of nanocarriers through oral, intravenous, and rectal routes presents distinctive technical challenges, encompassing aspects of biocompatibility, drug stability, mucosal barrier penetration, targeting specificity, abrupt drug release, and biocompatibility within the biological milieu. Oral administration necessitates addressing the intricate interplay between gastrointestinal barriers and bioavailability, alongside the constraints posed by intestinal mucosal permeability [208]. Intravenous delivery entails tackling issues encompassing plasma stability within the systemic circulation, dosage-dependent hepatic and splenic clearance of nanocarriers, as well as potential immunogenic reactions. Conversely, rectal administration mandates overcoming hurdles associated with the physicochemical and biochemical interactions at the colonic mucosa, alongside considerations of local immune responses. The formulation of nanocarriers necessitates meticulous consideration of these multifaceted factors to realize efficacious colonic targeting for therapeutic interventions.

In spite of the diverse array of therapeutic interventions available for UC, persistent limitations including non-specific drug effects, systemic adverse reactions, therapeutic resistance, and high relapse rates continue to pose challenges. To address these issues, potential strategies encompass the development of targeted delivery systems, wherein precise drug localization to inflammatory sites is achieved through the modification of drug molecules or carriers. Simultaneously, the exploration of combination therapies such as antioxidant/ROS scavenging treatments, gut microbiota modulation, and synergistic administration of classical anti-inflammatory and immunosuppressive agents may offer effective avenues to enhance therapeutic efficacy. Additionally, personalized treatment [209] regimens based on individual patient profiles,

coupled with controlled drug release technologies for sustained delivery, and real-time disease progression assessment through biomarker monitoring, could contribute to surpassing the efficacy of traditional approaches while minimizing adverse effects. These approaches hold promise for surpassing the limitations of conventional therapies, potentially enabling breakthroughs in the treatment of UC. However, these approaches require rigorous validation and further investigation in clinical practice to ensure their safety and efficacy.

Colon-targeted systems represent an innovative therapeutic strategy with significant potential in the treatment of UC. These systems offer promising avenues for enhanced therapeutic efficacy, reduced side effects, and personalized treatment through targeted therapy, improved stability and bioavailability. Nonetheless, the present status of colon-targeted systems primarily resides within the domain of research and development, and the successful transition of these designs into clinical practice encounters several challenges. From the disease perspective, current studies on the pathogenesis of UC are not sufficiently detailed and a large number of unknown molecules are involved in its pathology. This will require the introduction of more advanced technologies such as molecular docking, proteomic, transcriptomic and high-throughput screening to design, screen and identify more specific UC-related receptors, ligands, or biomarkers [165]. Additionally, more research is needed to answer questions such as whether altered microbiota causes UC or UC leads to altered microbiota, and how different micro/nanodrug delivery systems interact with the colonic flora and have an impact on the immune system of the gut [148]. From the perspective of delivery vehicles, it is essential to comprehensively understand their properties during gastrointestinal transport, including safety, stability, physical and surface chemistry, and absorption or binding mechanisms [152]. For example, derivatives of certain materials (e.g., CS), despite the low toxicity of their precursors, must be evaluated separately as new chemical entities [210]. Nanopreparations using simple and controlled preparation methods with good stability and reproducibility have considerable potential for translation. As these systems continue to undergo rigorous preclinical and clinical evaluations, they have the potential to revolutionize the treatment landscape of UC by providing amplified therapeutic effects, minimizing adverse reactions, and improving patient prognosis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2023.109074.

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