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Phytoconstituent-derived nano-medicines/vesicles providing a promising dawn for inflammatory bowel disease

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ABSTRACT

Natural phytoconstituents exhibit distinct advantages in the management and prevention of inflammatory bowel disease (IBD), attributed to their robust biological activity, multi-target effects, and elevated safety profile. Although promising, the clinical application of phytoconstituents have been impeded by poor water solubility, low oral bioavailability, and inadequate colonic targeting. Recent advancements in nanotechnology has offered prospective avenues for the application of phytoconstituents in the treatment of IBD. A common strategy involves encapsulating or conjugating phytoconstituents with nanocarriers to enhance their stability, prolong intestinal retention, and facilitate targeted delivery to colonic inflammatory tissues. Furthermore, drawing inspiration from the self-assembling nanostructures that emerge during the decoction process of Chinese herbs, a variety of natural active compounds-based nanoassemblies have been developed for the treatment of IBD. They exhibit high drug-loading capacities and surmount the challenges posed by poor water solubility and low bioavailability. Notably, phyto-derived nanovesicles, owing to their unique structure and biological functions, can serve as therapeutic agents or novel delivery vehicles for the treatment of IBD. Consequently, this review provides an extensive overview of emerging phytoconstituent-derived nano-medicines/vesicles for the treatment of IBD, intending to offer novel insights for the clinical management of IBD.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract (GI tract) including ulcerative colitis (UC) and Crohn's disease (CD), which can cause rectal bleeding, severe diarrhea, anemia, fever, malnutrition, and other debilitating symptoms that seriously affect patients' quality of life [1]. Over the past two decades, there has been a marked increase in the global incidence of IBD, which is anticipated to impose a substantial social and economic burden on governments and healthcare systems in the forthcoming years [2]. The pathological environment of IBD is primarily characterized by immune cell infiltration [3–5], elevated levels of inflammatory cytokines [5,6], compromised intestinal mucosal barrier function [7], high oxida-

tive stress [8,9] and dysbiosis of the gut microbiota [10–13]. In IBD patients, significant infiltration of immune cells such as T cells, B cells, and macrophages occurs within the intestinal mucosa. These immune cells play a pivotal role in the pathogenesis of IBD by releasing pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and IL-6, which contribute to intestinal inflammation. Furthermore, the intestinal mucosal barrier function is compromised in IBD patients, allowing for easier translocation of gut bacteria, toxins, and other substances into the bloodstream, thereby triggering a systemic inflammatory response. Additionally, the accumulation of high concentrations of ROS at the sites of intestinal lesions, coupled with an imbalance in the gut microbiota characterized by a decrease in beneficial bacteria and an increase in pathogenic bacteria, also constitutes a typical pathological feature of IBD. The current clinical therapeutic strategies primarily encompass the use of anti-inflammatory drugs (such as aminosalicic acid derivatives, corticosteroids), immunosuppressants (such as azathioprine, methotrexate), and biologics (such as anti-TNF- α monoclonal antibodies, interleukin

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receptor antagonists) to mitigate inflammatory responses [14,15]. In addition, modulating the balance of gut microbiota through probiotics and prebiotics to improve the gut environment represents an effective therapeutic strategy [16]. However, they are usually associated with long-term administration, limited efficacy, high relapse rates and severe side effects [17]. Thus, the development of novel therapeutic options that offer improved safety and efficacy remains a crucial objective in the field of IBD research.

Phytoconstituents always held a privileged position in drug development owing to their high activity, favorable safety profile, diverse therapeutic mechanisms, abundant sources, and cost-effectiveness [18–23]. Numerous studies have already demonstrated the potential of phytoconstituents in treating IBD [24–26]. Notably, several phytoconstituents have entered clinical trials for IBD treatment with promising outcomes. For instance, curcumin (CUR) has been used in clinical trials to evaluate its efficacy in preventing relapse in patients with IBD (ClinicalTrials.gov: NCT03122613, NCT02255370), as well as the tolerability of CUR in pediatric patients with IBD (ClinicalTrials.gov: NCT00889161). Furthermore, a clinical trial to determine whether berberine (BBR) could reduce the annual recurrence rate of UC in remission is in phase 4 (ClinicalTrials.gov: NCT02962245). Phytoconstituents that have progressed to clinical trials are listed in Table S1 (Supporting information). However, oral administration of natural active compounds often encounters challenges such as poor aqueous solubility, short plasma half-life, limited oral bioavailability, and nonspecific targeting, which significantly hinder their clinical applicability [27]. To circumvent these issues, the employment of innovative drug delivery systems represents a potential approach. With the advent of nanotechnology, various nanotechnology-based drug delivery systems (NDDSs), such as nanoparticles, liposomes, polymers, and hydrogels, have demonstrated the capacity to substantially enhance the aqueous solubility and bioavailability of botanical compounds [28–31]. Additionally, inflamed intestinal tissues exhibit an enhanced permeability and retention (EPR) effect due to disrupted mucosal layers, elevated numbers of macrophages and other immune cells, and compromised tight junctions between cells [32,33]. Consequently, these smaller-sized NDDSs tend to accumulate preferentially within inflamed tissues *via* the GI tract and are taken up by immune cells such as macrophages or dendritic cells, effectively delivering the therapeutic agents to the inflamed colonic tissue [34]. Moreover, NDDSs can be meticulously engineered to exploit the pathophysiological features of IBD, such as distinctive pH conditions, enzyme activities, redox microenvironments, and overexpressed receptors, thereby achieving targeted drug delivery to specific sites of inflammation within the colon.

Interestingly, several investigations have revealed the presence of nanoscale products during the decoction process of Chinese herbs [35–37]. This phenomenon is primarily attributed to the capacity of active monomeric constituents in Chinese herbs to self-assemble into nanostructures through non-covalent interactions such as hydrogen bonding, electrostatic force, van der Waals force, π - π stacking interaction and hydrophobic interaction [38,39]. Notably, these self-assembling nanostructures may be the key components in the efficacy of Chinese herbal decoctions, demonstrating augmented effectiveness at the same dose [35,37]. Furthermore, by circumventing the need for exogenous nanocarriers, these self-assembling nanostructures exhibit high drug encapsulation and hold promise for scalable production and clinical application. Building on these exciting findings, a variety of natural active compounds-based nanoassemblies have evolved as burgeoning and promising platforms for the therapeutic intervention of IBD [40–42].

Notably, phyto-derived nanovesicles (NVs) have recently gained attention as a promising therapeutic option for IBD. Composed of a phospholipid bilayer with an enclosed structure, these NVs encapsulate

a variety of bioactive constituents, including phospholipids, proteins, and nucleic acids. These biogenetically derived components have been found to regulate the inter-kingdom communication between the gut microbiota and the host immune system, thereby fostering antimicrobial immunity and promoting gastrointestinal well-being [43,44]. In addition, phyto-derived NVs often carry some bioactive small molecule compounds to exert anti-inflammatory and antioxidant effects [45]. Notably, as naturally-derived NVs, they possess numerous advantages over synthetic nanoparticles, such as a straightforward production process, good biocompatibility, non-immunogenicity, high stability, and extended circulation times [46–48]. Consequently, phyto-derived NVs offer a promising platform for the prevention and treatment of IBD, leveraging their inherent properties to address the complex pathophysiology of this chronic condition.

Given the crucial role of phytoconstituents in IBD, herein we comprehensively review the recent advances in these fields with the aim of generating new ideas for the development of effective treatments for IBD (Scheme 1). First, we outline the therapeutic mechanisms and challenges of phytoconstituents for the treatment of IBD. Second, we provide a comprehensive overview of phytoconstituent-derived nano-medicines/vesicles, including natural active compounds-loaded nanomedicines using nanocarriers, natural active compounds-based nanoassemblies and natural phyto-derived nanovesicles. Finally, we highlight the current limitations and future research directions of phytoconstituent-derived nano-medicines/vesicles.

2. Mechanisms and challenges of phytoconstituents in the treatment of IBD

2.1. The therapeutic mechanisms of phytoconstituents in the treatment of IBD

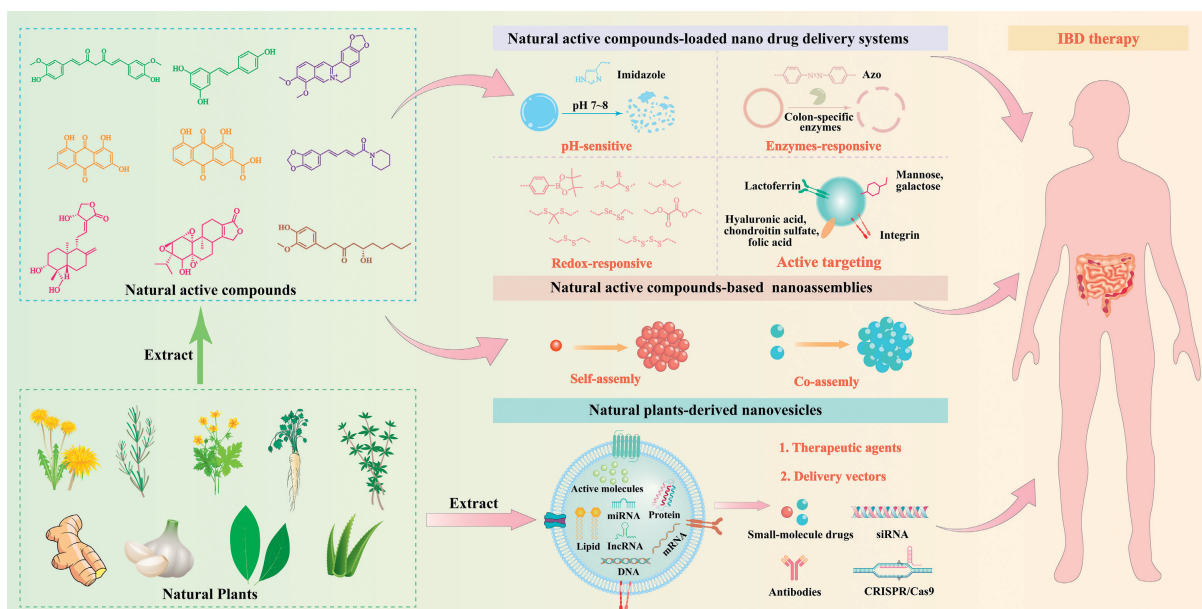
So far, numerous active ingredients in phytoconstituents (such as polyphenols, alkaloids, quinones and terpenoids) have been identified that exert a wide array of effects, such as regulating immunity, reducing inflammatory response and oxidative stress damage, regulating gut microbiota, and reinstating the integrity of the intestinal mucosal barrier, which can effectively control the occurrence and development of IBD [49]. Next, we will briefly describe the mechanisms by which phytoconstituents treat IBD (Table S2 in Supporting information).

2.1.1. Anti-inflammatory effect

Currently, the primary clinical strategy for alleviating IBD symptoms involves using medications that reduce inflammation. Consequently, phytoconstituents with significant anti-inflammatory effects are considered promising therapeutic agents for IBD. For instance, CUR, a naturally occurring polyphenol, demonstrates therapeutic effects in dextran sulfate sodium (DSS)-induced colitis model by modulating the Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88)/nuclear factor kappa-B (NF- κ B) and p38 mitogen-activated protein kinases (MAPK) signaling pathways, suppressing NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation, and down-regulating pro-inflammatory cytokines [50,51]. Similarly, the natural diterpene andrographolide has been shown to ameliorate DSS-induced intestinal barrier dysfunction and inflammation by inhibiting the NF- κ B and MAPK pathways in colon tissues and activating the adenosine 5'-monophosphate-activated protein kinase (AMPK) pathway [52].

2.1.2. Anti-oxidation effect

There is substantial evidence suggesting that reactive oxygen species (ROS) play a crucial role in the onset and progression of



Scheme 1. Schematic illustration of phytoconstituent-derived nano-medicines/vesicles as effective therapeutic reagents of IBD.

IBD [9,53-55]. ROS can disrupt signal transduction, provoke inflammation, damage the gastrointestinal mucosal layer, and facilitate bacterial invasion, ultimately leading to the development and exacerbation of IBD [56]. Oxidative stress and ROS overproduction are widely recognized mechanisms closely associated with IBD [9]. For instance, the natural polyphenol epigallocatechin-3-gallate (EGCG) enhances the expression of superoxide dismutase and glutathione peroxidase, thereby reducing ROS levels in inflamed tissues, effectively treating DSS-induced colitis in mice [57,58]. Additionally, Rhein activates the nuclear factor erythroid-2-related factor 2 (Nrf2)-heme oxygenase-1 (HO1)-NAD(P)H dehydrogenase quinone 1 (NQO1) pathway, inhibits the expression and translocation of the Nox2 subunit, and modulates redox balance to prevent acute colitis [59].

2.1.3. Regulating the immune system

IBD is an autoimmune disorder characterized by the immune system's erroneous attack on intestinal tissues, leading to inflammation and damage. The clinical treatment of IBD often involves the use of immunosuppressants such as azathioprine and methotrexate. Therefore, modulating the immune system is a critical strategy in managing IBD. Several phytoconstituents have been identified to significantly mitigate IBD by modulating immune responses. For instance, BBR, a renowned compound derived from *Coptis rhizoma*, has been shown to reduce the infiltration of neutrophils, macrophages, dendritic cells, and innate lymphoid cells in the colon, as well as regulate T helper (Th) 17 cells to restore immune balance in murine models of UC [60,61]. Triptolide has been reported to reduce the production of Th1 cytokines by inhibiting the TNF- α /tumor necrosis factor receptor 2 (TNFR2) signaling pathway in the colonic mucosa of IL-10 gene-deficient mice and attenuate the pro-inflammatory responses of Th17 cells by suppressing the IL-6/signal transducer and activator of transcription 3 (STAT3) pathway and the IL-23/IL-17 immune axis [62,63].

2.1.4. Regulating the gut microbiota

Dysbiosis of the gut microbiota plays a critical role in the onset and progression of IBD [64]. An imbalanced intestinal microbiome can lead to immune system dysfunction and impaired intestinal barrier function. Clinical studies have demonstrated that restoring

the balance of the intestinal microbiome can significantly alleviate IBD symptoms [65]. For instance, dihydromyricetin (DMY) has been shown to mitigate IBD in mouse models by enhancing the populations of beneficial bacteria, such as *Lactobacillus* and *Akkermansia* species, and restoring bile acid metabolism [66]. Resveratrol has been reported to diminish the population of acidic bacteroides, bolster the metabolism of short-chain fatty acids, elevate the concentration of butyric acid, and reestablish the gut microbiota at a stable equilibrium [67].

2.1.5. Restoring the intestinal barrier

When the intestinal barrier is compromised, harmful substances may translocate into harmful substances within the intestine may translocate into the bloodstream, potentially triggering a systemic inflammatory response. Consequently, safeguarding the intestinal barrier constitutes one of the pivotal strategies for the prevention and management of IBD. Luteolin has demonstrated efficacy in facilitating the restoration of intestinal barrier function in UC mice by elevating the levels of group 3 innate lymphoid cells expressing natural cytotoxic receptors and enhancing the expression of tight junction proteins zona occludens 1 (ZO-1) and occludin [68].

2.2. Challenges faced by phytoconstituents in the treatment of IBD

2.2.1. Poor water solubility and bioavailability

As shown in Table S2, natural active compounds such as polyphenols, alkaloids, terpenoids, and quinones possess predominantly nonpolar groups, resulting in pronounced hydrophobic characteristics and consequent low water solubility. Furthermore, certain natural active compounds, including polyphenolic compounds, can engage in intramolecular or intermolecular hydrogen bonding and π - π stacking interactions. These interactions disrupt their affinity with water molecules, further diminishing their solubility in aqueous environments. Additionally, in plants, the reduced water solubility aids in preserving the biological activity of these compounds by hindering their premature degradation or dilution within cellular compartments. Despite the promising potential of phytoconstituents in managing IBD, their therapeutic application remains restricted due to challenges related to poor solubility and oral bioavailability [69]. For example, CUR exhibits extremely low

water solubility ($\sim 1 \mu\text{g/mL}$), leading to its poor oral bioavailability [70]. In a human study, the peak plasma concentration of BBR was only $0.07 \pm 0.01 \text{ nmol/L}$ following a single oral dose of 500 mg administered to 10 volunteers [71].

2.2.2. GI tract environment

Since IBD is a chronic intestinal disease requiring long-term medication, oral administration is more acceptable to patients and more likely to reach the site of the lesion. However, the acidic environment of the GI tract, along with various enzymes present within it (such as pepsin and a multitude of digestive enzymes in the small intestine), can significantly impact the stability and bioavailability of natural active compounds [72]. For instance, following oral administration of CUR, it undergoes metabolism to form inactive CUR conjugates (CUR glucuronide and sulfates) or reduced metabolites (tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin) [73]. Additionally, the first-pass metabolism in the intestinal tract significantly impacts the clinical application of natural active compounds. One study demonstrated that upon oral administration of 100 mg/kg of berberine to rats, approximately half was eliminated in the small intestine, leading to a very low absolute oral bioavailability of 0.36% in rats [74].

2.2.3. Administration strategy

IBD can be managed through various administration approaches including oral, rectal, and topical routes. Among these, oral administration is the most commonly utilized. However, owing to the limited water solubility and low bioavailability of phytoconstituents, single dosing often necessitates large doses to achieve therapeutic effects, raising safety concerns. Furthermore, for chronic conditions like IBD, chronic therapy is typically required for symptom management. Nevertheless, patient adherence tends to be suboptimal with long-term intravenous or rectal administration.

3. Natural active compounds-loaded nanomedicines using nanocarriers

The delivery of natural active compounds through NDDSs have recently gained attention as a promising therapeutic option for IBD. The incorporation of natural active compounds into NDDSs offers a solution to inherent limitations, such as susceptibility to enzymatic degradation, hydrolysis in the harsh physiological environment of the GI tract, and challenges with bioavailability and targeted delivery to sites of colonic inflammation [75]. At present, researchers have designed different NDDSs according to the pathophysiological characteristics of IBD, which include distinctive pH levels in gastric fluid, elevated levels of ROS, and specific bacterial enzymes present in the intestines. These NDDSs can release natural active compounds in response to physiologically relevant stimuli at the inflammatory site of the colon, thereby delivering drugs specifically to the target site to exert therapeutic effects. Moreover, inflammatory colon tissue exhibits overexpressed receptors, adhesion molecules, and proteins on the surface of epithelial and immune cells [76,77]. NDDSs modified by relevant specific ligands/antibodies can actively target the inflammatory site, thus leading to superior therapeutic outcomes with reduced toxicity associated with systemic exposure [78]. This section provides a comprehensive overview of current oral NDDSs employed in the treatment of IBD, with the aspiration of offering novel perspectives for the efficient delivery of natural active compounds and advancing clinical drug development for IBD.

3.1. pH-sensitive nanomedicines

Considering the stringent physiological environment of the GI tract and the changes in pH in different areas (the stomach, pH

1.5–3.5, the small intestine, pH 5.5–6.8, and the large intestine, pH 7.0–8.0), simple NDDSs may not fulfill their mission of delivering drugs [79]. The pH-sensitive drug delivery system can be designed by coating a pH-sensitive biodegradable polymer on the surface of the drug carrier to target inflammatory sites in the colon. These polymers exhibit resistance to degradation in the stomach and small intestine, yet rapidly dissolve or swell to release the drug at specific pH values at the colon site.

Eudragit® S100, a pharmaceutical acrylic resin, is a commonly used polymer for colon drug delivery, which releases the drug only at specific pH in the colon [80]. In order to solve the problems of poor oral bioavailability, stability and inadequate colonic targeting of Glycyrrhizic acid (GA), Zeeshan *et al.* loaded GA into poly(lactico-glycolic acid) (PLGA) nanoparticles through double emulsion method and then coated them with pH-sensitive polymer Eudragit S100 [81]. The resulting GA-loaded ES100/PLGA nanoparticles remained stable in the upper GI tract while specifically releasing GA in the colon and prolonging its retention time. *In vivo* experimental results indicated that the nanoparticles could significantly improve IBD by reducing the inflammation of colon tissue and relieving oxidative stress. In one study, Wang *et al.* prepared emodin (EMO)-loaded PLGA/Eudragit® S100/montmorillonite nanoparticles (EMO/PSM NPs) using a multifunctional one-step assembly method [82]. The resulting EMO/PSM nanoparticles could release EMO at colonic pH and increase its retention time at the inflammatory site. Oral administration of EMO/PSM nanoparticles in UC mice reduced disease activity index (DAI), achieved histopathological remission, and mitigated colon inflammation. Furthermore, EMO facilitated mucosal barrier regeneration by upregulating the gene levels of tight junction proteins (including claudin-2, occludin, and zonule-1) and mucin2. These results demonstrated that Eudragit® S100 can be used for colon-targeted delivery of natural active compounds, thereby improving their bioavailability and anti-IBD efficacy.

Chitosan and alginate are natural polysaccharides extracted from the sea, which exhibit good mucous membrane adhesion, biodegradability, and biocompatibility, making them ideal for the shell of oral preparations [83,84]. The carboxyl group of alginate and the amino group of chitosan create a strong electrostatic interaction that causes them to contract and form gels at low pH, thus protecting the drug from GI tract and the aggressive stomach environment, whereas rapid swelling releases the drug in a neutral environment [85]. Oshi *et al.* used multilayer chitosan/alginate membranes to encapsulate CUR nanocrystals for targeted drug delivery to improve the bioavailability of CUR [86]. The experimental results showed that the CUR nanoparticles exhibited minimal drug release within the gastric and small intestinal environments, whereas they facilitated a rapid drug release profile in the colonic region. Confocal imaging and fluorescence quantification of mouse colonic tissue demonstrated the preferential accumulation of CUR nanoparticles in inflamed colonic tissues. Zhou *et al.* have developed a dextran-functionalized PLGA nanoparticles to effectively load andrographolide (AG) and a carbon monoxide donor (CORM-2). Further, a chitosan/alginate hydrogel was used to encapsulate the outer layer. The resulting AG/CORM-2@NP-Dex could stably pass through the upper GI tract, then preferentially target and release the drug in the inflamed colon [87]. *In vitro* and *in vivo* experiments have shown that AG/CORM-2@NP-Dex exhibits synergistic alleviation of UC and has a high safety profile. Furthermore, some studies have demonstrated that fucoidan and pectin both possess pH-responsive capabilities, enabling targeted drug delivery to colonic lesion sites (Supporting information).

3.2. Enzymes-responsive nanomedicines

The terminal ileum and colon harbor a diverse array of aerobic and anaerobic microorganisms, numbering over 400 species, which

are capable of producing a multitude of hydrolytic and reductolytic enzymes such as azo reductase, polysaccharide enzyme, and nitroreductase [88–90]. These enzymes can be involved in xenobiotic metabolism and drug activation. Zhang *et al.* coassembled synthetic azo reduction-responsive polymers (PEG-Azo-PLGA) and mucosa-adhered polymers (catechol-modified D- α -tocopherol polyethylene glycol succinate, TPGS) into nanomicelles for colon-targeted delivery of CUR [91]. The *in vitro* release results showed that the release of CUR nanomicelles in rat colon fluid was significantly faster than that in PBS, indicating that CUR nanomicelles could release drugs under the action of azo reductase. In addition, the cellular uptake capacity of CUR-micelles was significantly higher than that of free CUR in Caco-2 cells. In the DSS-induced colitis mouse model, CUR-micelles could significantly reduce the symptoms of colitis by remodeling gut microbiota, regulating TLR4/MyD88/NF- κ B signaling pathway and reducing the expression levels of pro-inflammatory cytokines (MPO, IL-6, IL-1 β and TNF- α). In addition, several polysaccharides such as amylose, cyclodextrin, dextran, and pectin belong to enzyme sensitive polymers that remain stable in the stomach and small intestine and are degraded by the corresponding hydrolytic enzymes in the colon to release the encapsulated cargo [92].

Yeast cell wall microparticles (YPs) are an excellent oral drug carrier due to their rigid peptidoglycan layer, which can protect drugs through the stomach and small intestine. Once reach the colon, the main component of YPs, β -1,3-D-glucan, can be rapidly degraded by β -glucanase to release the drug. In one study, rhein (RH)-loaded OVA nanoparticles were embedded with YPs to overcome the limitations of RH insolubility, low bioavailability, and poor colon targeting [93]. The *in vitro* drug release results showed that the drug release of the preparation in the presence of 0.5% β -glucanase was significantly faster than that in PBS. Scanning electron microscopy images revealed that the preparation was incomplete and fragmented under 0.5% β -glucanase. These results demonstrated that YPs can achieve targeted release in response to β -glucanase and is a good oral delivery system for UC treatment. Additionally, a soluble dietary fiber extracted from wheat, known as nutrose, has been discovered to serve as an enzyme-responsive tool for colonic drug delivery (Supporting information).

3.3. Redox-responsive nanomedicines

Given the accumulation of high concentrations of ROS in the pathological regions of IBD, the development of ROS-sensitive drug delivery systems represents a promising IBD targeting strategy. Currently, the introduction of ROS-responsive groups (such as 4-(hydroxymethyl)phenylboronic acid pinacol ester, thioether, thioke-tal, diselenide and peroxalate ester bonds) into drug delivery systems has emerged as a mature strategy for intelligent drug delivery [94]. Genistein (GEN) is a natural isoflavone compound derived from soybean that exhibits remarkable anti-inflammatory and antioxidant effects [95]. Previous studies have demonstrated its potential as a therapeutic agent for IBD [96–99]. To address the challenges of limited water solubility, low oral bioavailability and rapid metabolism, Fan *et al.* developed a novel ROS-responsive nanomaterial (GEN NP2) containing a GEN modified with superoxide dismutase-mimetic temporally conjugated β -cyclodextrin and 4-(hydroxymethyl)phenylboronic acid pinacol ester for the enteritis site-specific delivery of GEN and for improving the stability and bioavailability of GEN in the GI tract [100]. When incubated with 10 mmol/L H₂O₂, the nanoparticles could be well hydrolyzed and released in a time-dependent manner and concentration-dependent manner. In DSS-induced UC mouse models, oral administration of GEN NP2 effectively alleviated oxidative stress and inflammatory infiltration by regulating the autophagy-inflammasome pathway through estrogen receptor β (ER β) activation. Notably,

Liang *et al.* synthesized a ROS ultra-sensitive polymer containing diselenide and oxalate ester bonds for the targeted delivery of CUR. This polymer protected CUR from oxidative degradation (about 4-fold higher than free CUR) and could rapidly release CUR in response to an oxidative microenvironment, significantly enhancing its *in vitro* antioxidant activity and anti-inflammatory effects [101]. In a murine colitis model, oral administration of the obtained SeOC NP reshaped the gut microbiota and substantially alleviated IBD symptoms. Luteolin (LUT) is a natural flavonoid and can alleviate colitis by regulating the intestinal microbiota, suppressing cell apoptosis and autophagy through anti-inflammatory effects. However, LUT's poor water solubility and low bioavailability limit its further application. Therefore, Tan *et al.* synthesized a polymer TPGS-*b*-poly(β -thioester) with ROS-responsive thiol for targeted delivery of LUT to exert a better therapeutic effect [102]. The obtained LUT nanopolymer could release LUT in response to the high concentration of ROS in the inflammatory site of colon to eliminate ROS, inhibit inflammatory infiltration, regulate the immune microenvironment, and restore the mucosal barrier to alleviate UC.

Although the colonic inflammatory site microenvironment is highly oxidative, the intracellular compartment is in a reduced state. At the same time, the inflammatory process also stimulates macrophages to produce more Glutathione (GSH) to combat intracellular oxidative stress [103,104]. Therefore, novel reduction-responsive NDDSs are developed for targeted drug delivery to the colonic inflammatory site. EGCG, the primary active polyphenol component in green tea, which possesses potent anti-inflammatory and antioxidant properties [105]. Although previous studies have demonstrated good efficacy on a mouse model of IBD, considerable challenges have been the poor stability and low oral bioavailability of EGCG [106–108]. To this end, Gou *et al.* successfully loaded EGCG into ovalbumin (OVA) by gentle heating method with a high drug encapsulation efficiency (98.1%) [103]. Due to the sulfhydryl/disulfide bond in OVA, EGCG-NPs can rapidly release drugs in response to GSH in inflammatory colon cells. The results of the pharmacological study demonstrated that EGCG-NPs significantly inhibited the production of pro-inflammatory cytokines, while simultaneously enhancing the levels of anti-inflammatory cytokines, thereby alleviating the symptoms of colitis in mice. To address the issues of poor water solubility, photosensitivity, and low bioavailability of cannabidiol (CBD), Zhang *et al.* synthesized a GSH-responsive mitochondrial/colon dual targeting polymer using inulinosin, α -lipoic acid (α -LA), and bromide-(5-carboxypentyl)triphenylphosphine (TPP) as raw materials for targeted delivery of CBD. The experimental results showed that the constructed CBD nanoparticles exhibited excellent mitochondrial targeting ability and could be rapidly released at 10 mmol/L GSH concentration. In addition, oral administration of CBD nanoparticles significantly alleviated the symptoms of DSS-induced colitis in mice by regulating TLR4-NF- κ B signaling pathway, alleviating oxidative stress, restoring intestinal mucosal barrier function and intestinal mucosal permeability, and regulating gut microbiota [109].

3.4. Receptor-mediated active targeted nanomedicines

During the occurrence of IBD, certain receptors, adhesion molecules and proteins (such as CD44, CD98, folate receptor) are overexpressed on the surface of colon epithelial cells and immune cells at the site of colonic inflammation [76]. Therefore, targeting these overexpressed proteins with ligand/antibody-modified drug delivery systems provides a promising strategy for targeted delivery of drugs to treat IBD.

CD44 is a transmembrane glycoprotein that is significantly overexpressed on the surface of activated macrophages in colitis tissue [110]. The common ligands of CD44 include hyaluronic acid

(HA), fibronectin, sericin, chondroitin sulfate (CS), *etc.* HA and CS are often used for surface functionalization of delivery vectors to specifically target drug delivery to colonic lesions. Magnolol (Mag) is a kind of biphenol compound isolated from *Magnolia officinalis*, which has been proved to play an excellent therapeutic effect on UC by regulating the MAPK, NF- κ B and peroxisome proliferator-activated receptor γ (PPAR- γ) anti-inflammatory signaling pathways, inhibiting Th17 cell differentiation by activating SIRT3 [111–113]. Wang *et al.* loaded Mag into core-shell nanoparticles (Mag@CS-Zein NPs) of zein with CS functionalized to improve its oral bioavailability and targeting ability to inflammatory colonic lesions. Cellular uptake assay showed that Mag@CS-Zein NPs could actively target CD44 receptor and enter macrophages through endocytosis to play an anti-inflammatory effect [114]. Oral administration of Mag@CS-Zein NPs could significantly alleviate the symptoms of DSS-induced colitis in mice through anti-inflammation and repair of intestinal mucosal barrier. Pterostilbene (PS) is an active ingredient from *Pterocarpus indicus* Willd., blueberry and grape, exhibiting antioxidant and anti-inflammatory properties [115]. Previous studies have demonstrated the potential of PS in alleviating colitis symptoms in murine models by mitigating inflammation, suppressing TNF- α expression, and inhibiting intestinal fibrosis [116,117]. To enhance the colon-targeting efficacy of PS, Wei *et al.* constructed an HA-modified L-Arg-based pH-activated nano-bomb system loaded with PS (HA-PS@NPs) [118]. HA-PS@NPs exhibited favorable biocompatibility and were capable of producing a pH-activated nano-bomb effect by generating CO₂ at lysosomal pH, thereby facilitating the cytoplasmic delivery of PS. *In vivo* imaging in mice showed that HA-PS@NPs had a stronger fluorescence signal than PS@NPs in healthy mice and colitis mice, demonstrating the ability of HA-mediated specific targeting to sites of colonic inflammation. In DSS-induced mouse model of colitis, oral administration of HA-PS@NPs significantly ameliorated UC symptoms by reducing intestinal permeability, downregulating pro-inflammatory cytokines, and improving the disease histopathology.

Folate receptor is a class of cell surface receptor glycoproteins that have been shown to be overexpressed in inflammatory tissues of the colon [119]. Chicoric acid (CA) is a polyphenolic compound in chicory and *Echinacea* with immune-enhancing and anti-inflammatory activities. In order to enhance the targeting ability of CA to colonic lesions, Yang *et al.* prepared folate (FA)-functionalized CA liposomes, which could actively target the macrophage-specific folate receptor, promote the polarization of M1 macrophages to M2 macrophages, and inhibit inflammatory response. *In vivo* experiments showed that FA/CA-liposomes effectively alleviated the pathological symptoms of UC mice [120]. Resveratrol (Res) has been proven to prevent and improve IBD through anti-inflammatory antioxidant and immune regulation [121]. Naserifar *et al.* has developed FA-conjugated PLGA nanoparticles (PLGA-FA-Res) that specifically recognize folate receptor in colitis tissues to initiate cellular endocytosis [122]. *In vitro* permeability results showed that PLGA-FA-Res almost penetrated into Caco-2 cells within 3 h, which was significantly greater than the trans-well permeability of PLGA-Res. In addition, Wu *et al.* encapsulated GA-loaded FA-Zein nanoparticles (GA@Pec-FA-ZeinNPs) with pectin to improve the stability and targeting ability of GA [123]. *In vitro* experiments showed that GA@Pec-FA-Zein NPs could bind to Folate receptor- β on the surface of colon cells to achieve targeted drug delivery. In DSS-induced UC mouse model, oral administration of GA@Pec-FA-Zein NPs could specifically adhere to the colon to exert anti-inflammatory and tissue recovery effects. Notably, targeting the mannose receptor, macrophage galactose C-type lectin, and low-density lipoprotein receptor-related protein, which are highly expressed in colonic inflammatory sites, also represents a promising drug delivery strategy (Supporting information).

3.5. Dual/multiple bioresponsive nanomedicines

3.5.1. pH/redox dual-responsive nanomedicines

Rutin, a natural flavonoid ubiquitously found in various plants, possesses a myriad of pharmacological properties, including anti-inflammatory, hypoglycemic, antioxidant, and neuroprotective effects [124]. Notably, rutin has been shown to ameliorate DSS-induced colitis by suppressing the expression of pro-inflammatory cytokines [125]. Despite its therapeutic potential, the clinical application of rutin is hindered by its poor solubility, membrane permeability, and stability [126]. To enhance the bioavailability of rutin *in vivo*, Wang *et al.* engineered a guanyl phenylborate saline gel (GBR) that incorporates rutin through encapsulates rutin *via* borate bonding and facilitates drug release in response to microenvironmental changes in inflamed tissues (Fig. 1A). The hydrogel exhibited stability in physiological conditions and achieved nearly complete drug release in weakly acidic and ROS-rich media, enabling a dual pH/ROS-responsive release mechanism [127]. In cellular studies, the GBR hydrogel demonstrated biocompatibility with normal cells, promoted cell aggregation and proliferation, and exhibited high safety. In the DSS-induced colitis model, the GBR hydrogel significantly inhibited the expression of the inflammatory cytokines TNF- α and IL-6, and displayed superior therapeutic efficacy compared to free rutin. In a related development, Qi *et al.* devised a dual pH/ROS-sensitive oral polysaccharide nanodelivery system (RH-F/C NPs), wherein chitosan provided pH sensitivity and fucoidan was covalently conjugated with hydroxymethylphenylboronic acid pinacol ester for ROS sensitivity [128]. *In vitro* simulated release assay, RH-F/C NPs showed good stability in the stomach and small intestine, while rapidly releasing drugs in the colon. Simulated release assays revealed that RH-F/C NPs maintained stability in the stomach and small intestine while allowing rapid drug release in the colon. Moreover, the release of RH-F/C NPs was accelerated in H₂O₂ solution as compared to simulated colonic fluid alone. In DSS-induced UC mice model, RH-F/C NPs significantly alleviated UC symptoms by reducing inflammation, decreasing oxidative stress, repairing the colonic mucosal barrier, and modulating intestinal microflora, achieving a "four-birds-with-one-stone" effect.

Fan *et al.* developed a colonic pH/GSH dual-responsive polymer nanoplatform for the delivery of Mag as a therapeutic agent against IBD [129]. The polymer matrix is constructed from poly(ethylene glycol)-*b*-polymethacrylate, which serves as a backbone and is conjugated with butyrate *via* a redox-sensitive disulfide linkage, enabling the self-assembly into nanoparticles (Fig. 1B). By optimizing the ratio of the main chain to the linker, the obtained PSBA-63@Mag was adept at responding to the neutral pH environment of the colon and liberating Mag and butyrate under intracellular reducing conditions. Ensuing experiments have corroborated that the dual-responsive PSBA@Mag could reduce the levels of inflammation and oxidative stress, regulate gut microbiota, repair the damaged mucosal barrier, and substantially ameliorate the clinical manifestations of IBD mice. In a separate investigation, Xu *et al.* synthesized a pH/GSH dual-responsive polymer for the delivery of ginsenoside Rh2 (a natural triterpenoid saponin compound with excellent anti-inflammatory and antioxidant properties) by utilizing *Angelica sinensis* polysaccharides (ASPs) as the main chain, functionalized with pH-responsive uracil acid and redox-responsive α -LA [131]. Experimental outcomes indicated that the Rh2/LA-UASP nanoparticles were capable of achieving dual-stimuli drug release in response to pH variations and redox potentials, and they demonstrated potent lysosomal escape mechanisms. In DSS-induced UC mouse model, oral administration of Rh2/LA-UASP nanoparticles significantly diminished inflammation, restored intestinal microbial equilibrium, and mitigated UC symptoms.

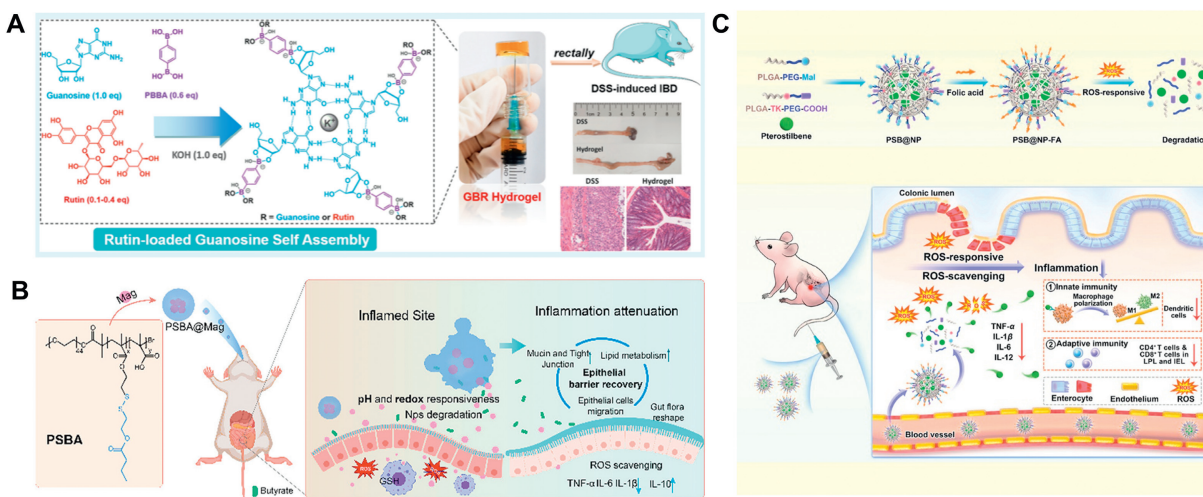


Fig. 1. Natural active compounds-loaded dual-responsive nanomedicines. (A) Rutin-loaded pH/ROS dual responsive hydrogel for the treatment of IBD. (B) Magnolol-incorporated pH/GSH dual responsive butyrate-based polymeric nanoparticles to treat IBD by improving epithelial barrier repair and inflammation mitigation. (C) Pterostilbene-loaded macrophages targeting /ROS-responsive nanoparticles ameliorate murine colitis by intervening colonic innate and adaptive immune responses. (A) Copied with permission [127]. Copyright 2022, American Chemical Society. (B) Copied with permission [129]. Copyright 2024, American Chemical Society. (C) Copied with permission [130]. Copyright 2023, Elsevier.

3.5.2. Macrophages targeting/redox response nanomedicines

Yan *et al.* developed a macrophage-targeted and ROS-responsive delivery system for the intelligent delivery of pterostilbene for the treatment of UC, by incorporating FA and ROS-sensitive thioketal into PLGA nanoparticles (Fig. 1C). The resulting PSB@NP-FA can be effectively internalized by RAW 264.7 and Colon-26 cells via CD44 targeting and preferentially localizes to the inflamed colon, subsequently responding to high concentrations of ROS at the site to release the drug, thereby exerting anti-inflammatory and anti-oxidative stress effects [130]. Interestingly, Jiang *et al.* fabricated tetrasulfide-containing organosilica nanoparticles (DSMSNs) and further functionalized the surface CS for oral targeted delivery of Res. Experimental findings indicated the DSMSNs@Res@CS could target CD44, which is highly expressed in inflamed colon tissue, and subsequently accumulate in intestinal epithelial cells and macrophages, while rapidly lyse and release Res in response to excessive GSH [132]. Oral administration of DSMSNs@Res@CS effectively ameliorated colonic inflammation and reestablished intestinal microbiota equilibrium in murine model of colitis, highlighting the potential utility of organosilicon nanoparticles as an oral drug delivery platform for the management of IBD.

3.5.3. Multiple bioresponsive nanomedicines

Luo *et al.* developed a colon-targeted smart delivery system using calcium pectin (CP) and HA dual-functional coatings around LF nanoparticles for the delivery of RH [133]. The resulting CP/HA/RH NPs effectively preserved the contents through the GI tract, with the outer layer of CP being selectively degraded by colon-specific enzymes to release the encapsulated payload upon reaching the colon. Subsequently, the synergistic action of HA and LF enhanced the specific targeting and absorption of the drug (Fig. 2A). In DSS-induced UC mice, oral administration CP/HA/RH NPs effectively inhibited the TLR4/MyD88/NF- κ B signaling pathway, significantly ameliorating inflammation and expediting colonic tissue repair. In another study, Xu *et al.* designed an enzyme/ROS-responsive and macrophages-targeted supramolecular drug delivery system to deliver rhein by introducing ROS-responsive thiodiglycolic anhydride and CD44-actively targeting HA into CD (Fig. 2B). The resulting HA-CsT@RH NPs exhibited minimal drug release within the gastric environment, whereas enabled a rapid drug release under 1 mg/mL β -glucosidase and high ROS conditions [134]. Cellular up-

take experiments revealed that HA-CsT@RH NPs were internalized by macrophages at a rate 1.5 times higher than that of non-HA-modified nanoparticles. Mechanistic explorations elucidated that HA-CsT@RH NPs exerted anti-inflammatory and anti-oxidative effects by regulating TLR4/NF- κ B p65 and Nrf2/HO-1 signaling pathways. Collectively, these findings underscore the potential of this multi-bioresponsive nanodelivery platform as an innovative therapeutic strategy for IBD. Additionally, Han *et al.* conjugated such pH/ROS-sensitive moieties as β -aminoester (PBAE) and thioglycolic anhydride to β -cyclodextrin and modified adamantane with Man, subsequently forming a multi-bioresponsive supramolecular nano system through host-guest interactions for the oral delivery of CUR [135]. To further enhance the gastrointestinal stability and colonic adhesion capabilities of Man-CUR NPs, they were additionally encapsulated within YPs. Experimental evidence indicated that the Man-CUR NYPs possessed excellent gastrointestinal stability and were capable of rapidly releasing the encapsulated CUR under conditions of neutral pH, 1 mmol/L H_2O_2 , and 0.5% β -glucanase. As expected, Man-CUR NYPs exhibited an enhanced ability to target colonic macrophages. In a DSS-induced murine colitis model, treatment with Man-CUR NYPs mitigated inflammation and oxidative stress by modulating the TLR4/NF- κ B and Nrf2/HO-1 pathways, facilitated the polarization of macrophages towards an anti-inflammatory phenotype, and ameliorated symptoms of UC.

Silk fibroin is a Food and Drug Administration (FDA)-approved polymer. The α -helical motifs, β -sheets, an abundance of amino groups and disulfide bonds within its architecture synergistically endow silk fibroin with the capacity for efficient cargo molecule encapsulation and its sensitivity to pH, ROS and GSH abnormalities [137]. In one study, Professor Xiao Bo's research Group used silk fibroin to encapsulate CUR and surface functionalize with CS to develop a multiple bioresponsive nanoparticles. As expected, these nanoparticles could target macrophages via CS and release CUR on demand in response to inflammatory colonic site pH with excess ROS. In a mouse model of colitis, these NPs significantly alleviated UC symptoms by either oral or intravenous administration [138]. In another study, they used another silk fibroin-*Antheraea pernyi* silk fibroin for the delivery of Res (Fig. 2C) [136]. Notably, except for the inherent pH and Redox sensitivity (Fig. 2D), the arginine-glycine-aspartate (RGD) tripeptides motifs abundant in *Antheraea pernyi* silk fibroin (ApSF) can selectively bind integrin receptors

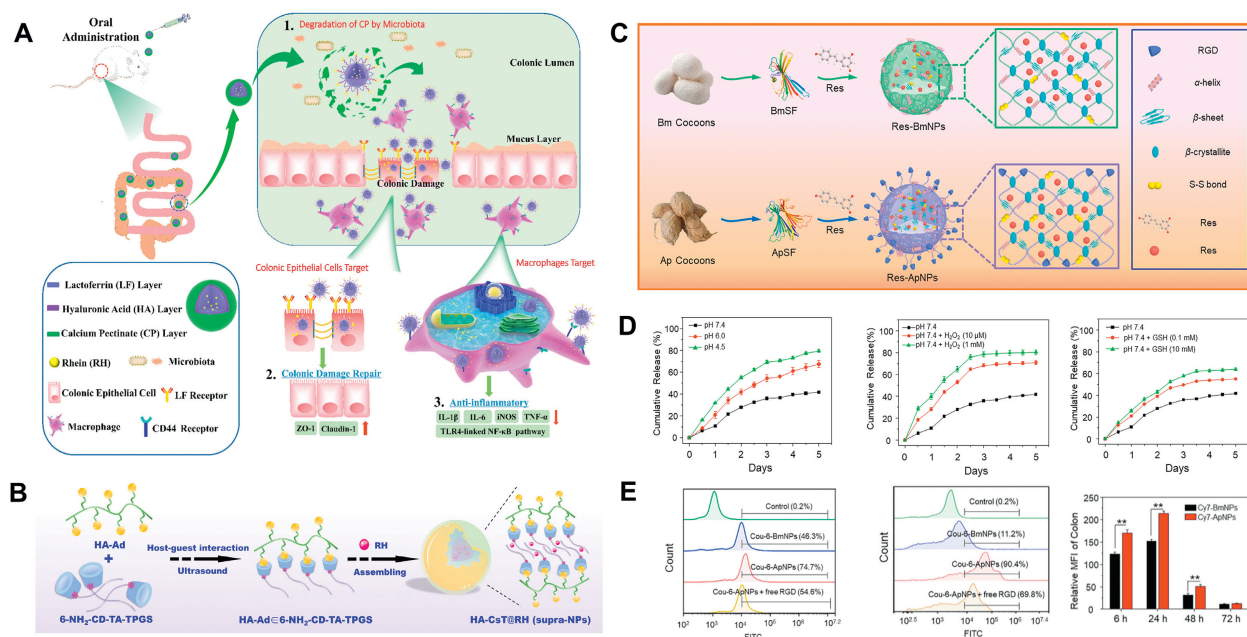


Fig. 2. Natural active compounds-loaded multi-bioresponsive nanomedicines. (A) Calcium pectinate and hyaluronic acid modified lactoferrin nanoparticles loaded rhein with enzyme-sensitive and dual-targeting for UC treatment. (B) Schematic diagram of the preparation of enzyme/ROS-responsive and macrophages-targeted HA-Cst@RH supramolecular for UC treatment. (C) Oral pH/redox-responsive and macrophages-targeted nanotherapeutics based on *Antheraea pernyi* silk fibroin for synergistic treatment of UC. (D) ApNPs at pH 7.4, 6.0, and 4.5, with H₂O₂ (pH 7.4), and GSH (pH 7.4). Data are mean $\pm$ S.E.M. (n = 3). (E) Flow cytometry histograms of internalization of Cou-6-BmNPs, Cou-6-ApNPs, and Cou-6-ApNPs in the presence of free RGD at an equal concentration of Cou-6 (0.03 μ g/mL) by CT-26 cells and Raw 264.7 cells after incubation for 2 h, quantitation of fluorescence intensities of colons from mice treated with hydrogel-embedding Cy7-BmNPs and Cy7-ApNPs at 6, 24, 48, and 72 h. Data are mean $\pm$ S.E.M. (n = 3; *P < 0.05, **P < 0.01). (A) Copied with permission [133]. Copyright 2021, Elsevier. (B) Reproduced with permission [134]. Copyright 2023, Elsevier. (C-E) Reproduced with permission [136]. Copyright 2022, Elsevier.

that are highly expressed on the plasma membrane of colonic epithelial cells and macrophages in inflamed colonic tissues, facilitating targeted drug delivery [139,140]. The cellular uptake assay showed that the uptake rate of ApSF by CT26 cells and Raw 264.7 macrophages was significantly higher than that of Bombyx mori SF (BmSF) without RGD, which was attributed to the targeting ability of RGD in ApSF to the overexpressed integrin in colitis tissue (Fig. 2E). The *in vivo* distribution experiment yielded similar results, with the colon fluorescence intensity being significantly higher in the Cy7-ApNP group compared to the Cy7-BmNP group. Additionally, Res-ApNPs significantly reduced intracellular levels of TNF- α and ROS, and promoted the polarization of macrophages to the M2 anti-inflammatory phenotype. In the DSS-induced murine model, oral administration of Res-ApNPs effectively mitigated inflammation and oxidative stress, repaired the epithelial barrier, reestablished the equilibrium of the colonic microbiome, and substantially ameliorated the clinical symptoms of UC.

3.6. Other nanomedicines

In addition to the aforementioned passive and active targeted delivery systems, various innovative nanodelivery platforms have also been employed for the oral administration of natural bioactive molecules (Supporting information).

In conclusion, the utilization of bioresponsive nanocarriers not only enhances the oral bioavailability of natural active compounds but also facilitates intelligent drug release and precise targeting, thereby achieving optimal therapeutic outcomes in IBD. However, the fabrication of NDDSs is a complex process, demanding meticulous control over characterization parameters to ensure stability and bioavailability. This intricacy contributes to increased production costs and technical challenges. Moreover, the use of certain nanocarrier materials may trigger immune reactions or toxicity concerns. Additionally, the *in vivo* fate of NDDSs

warrants attention [141]. As some nanomedicines may accumulate in the body, potentially posing health risks. Hence, rigorous quality assurance and comprehensive safety evaluations of natural active compounds-loaded NDDSs will be essential for future advancements.

4. Natural active compounds-based nanoassemblies

In 2008, scholars noted the presence of aggregates in traditional Chinese medicine decoctions, suggesting their potential as key components [142,143]. Recent investigations have identified nanoparticles in several traditional Chinese herbal formulas, such as Baihu decoction [144], Gegen-Qinlian decoction [145], and Qi Yin San Liang San Decoction [37]. Subsequent experiments have confirmed that these nanoparticles may be key components contributing to the therapeutic effects of these herbal formulations. However, the composition of these nanoparticles remains unclear, with only the main ingredients often being analyzable. Therefore, inspired by the self-assembled nanostructures that emerge during the decoction process of Chinese herbs, a variety of natural active compounds-based nanoassemblies with well-defined structures have been developed for the treatment of IBD. Single natural active compounds can form nano self-assemblies through hydrophobic interactions by introducing hydrophilic fragments into the structure [146,147] or within the system [148], or through supramolecular interactions [40,41]. These nanoassemblies offer high stability, enhanced oral bioavailability, and exceptional drug-loading capacity. Furthermore, drawing upon the principles of Chinese herb pair theory, some studies have revealed that two natural active compounds can coalesce into nanoassemblies through non-covalent interactions such as hydrogen bonding, electrostatic force, van der Waals force, π - π stacking interaction and hydrophobic interaction [42,149]. Owing to the incorporation of dual active ingredients, these natural active compounds-based binary nanoassem-

blies exhibit advantages including enhanced biological activity and multifunctional capabilities. Given their promising therapeutic potential and development prospects, we next summarize the research on natural active compounds-based nanoassemblies for the treatment of IBD.

4.1. Single natural active compounds-based nanoassemblies

Rosmarinic acid (RA) is a natural polyphenol compound isolated from the plants Rosemary, which has anti-inflammatory, antioxidant, anticancer, antibacterial and other pharmacological activities [150]. Previous research has shown that RA alleviated DSS-induced colitis in mice by inhibiting the activation of NF- κ B and STAT3 [151,152]. However, the high rate of gastrointestinal degradation associated with oral administration has hindered further application of RA [153]. To address this issue, Chung *et al.* incorporated hydrophilic PEG into RA, which facilitated the subsequent self-assembly into ROS-sensitive RA nanoparticles (RANPs) [146]. Compelling evidence from experiments indicated that RANPs exhibited a propensity for targeted accumulation within inflamed colonic regions and disintegrated under high ROS concentrations to liberate encapsulated therapeutic agents, thereby mitigating oxidative stress. In DSS-induced colitis mice, intravenous administration of RANPs effectively quelled the expression and secretion of pro-inflammatory cytokines in the affected colonic tissue, resulting in a marked amelioration of symptoms associated with UC. Interestingly, RANPs also demonstrated utility as a targeted drug delivery system, capable of encapsulating up to approximately ~16.5 wt% of dexamethasone.

BBR is an alkaloid extracted from Chinese medicinal plant *Coptis chinensis* Franch., which has been used in clinical practice. Its therapeutic potential in treating UC has been attributed to its antioxidant, anti-inflammatory, bacteriostatic, epithelial barrier protection, spasmolysis, and modulation of IBD-specific T cell imbalance properties [154–157]. To improve its pharmacokinetic profile, Zhao *et al.* synthesized a ROS-responsive prodrug by conjugating BBR with phenylboronic acid-functionalized carboxymethyl chitosan (Fig. 3A). This ingeniously designed prodrug can self-organize into nano-micellar structures (OC-B-BBR), which exhibit robust physiological stability and are equipped for rapid drug release under conditions of ROS abundance, thereby enabling efficient targeted delivery to the inflamed tissues of the colon [147]. In DSS-induced colitis mice, the OC-B-BBR formulation has been shown to downregulate pro-inflammatory cytokine expression, modulate the intestinal microbiota, and effectively mitigate the clinical manifestations of UC.

Interestingly, some studies have found that certain natural active compounds (such as ferulic acid and caffeic acid), could self-assemble into nanostructures [158–160]. In addition to exhibiting excellent bioactivity, they can also serve as carriers for drug delivery. Ferulic acid is a class of phyto-derived phenolic acids that possesses remarkable anti-inflammatory and antioxidant properties. Zhao *et al.* discovered that ferulic acid can be oxidized by the horseradish peroxidase/hydrogen peroxide system to yield single-electron delocalized intermediates. These intermediates subsequently cross-couple to form lignin and then undergo self-assembly to produce ferulic acid nanoparticles (FALNPs) (Fig. 3B). Owing to the weakly acidic carboxyl and hydroxyl groups present in the ferulic acid structure, FALNPs exhibited stability under strongly acidic conditions but dissociate under alkaline conditions, enabling targeted drug release specifically at sites of intestinal inflammation (Fig. 3C). Further investigations revealed that FALNPs mitigated intestinal inflammation by diminishing ROS levels, curtailing the expression of pro-inflammatory cytokines, and modulating the intestinal microbiome [40]. Notably, FALNPs could also be non-covalently loaded with chemotherapeutic agents and

are responsive to intestinal pH for release, thereby enhancing therapeutic efficacy (Fig. 3C).

In an investigative study, researchers prepared supramolecular nanoribbons (SNRs) of Que with an average length of approximately 13.91 μ m and 219 nm in width by employing a straightforward blending of a Que solution in DMSO with aqueous media (Figs. 3D and E). The SNRs assembly was attributed to the synergistic effects of hydrogen bonding and π - π stacking interactions among Que molecules, culminating in an exceptionally high drug encapsulation efficiency (approaching 100%) and robust stability within the GI tract [41]. Further experimentation elucidated that the Que SNRs possess the capability to selectively anchor to inflamed colon tissues via electrostatic engagement (Fig. 3F), whilst exhibiting remarkable antioxidant properties. In ionizing radiation and DSS-induced mouse model of colitis, the Que SNRs demonstrated commendable protective and therapeutic efficacy, such as the recovery of normal body weight and intestinal length, as well as the reduction of DAI score (Fig. 3G). This Que supramolecular nanopatform with straightforward and expeditious fabrication process coupled with a high drug payload holds considerable potential for clinical translation.

DMY is a natural phenolic compound found in several plants, including vine tea (*Ampelopsis grossedentata*), mulberry leaves and rhubarb [161]. Recent study indicated that DMY ameliorates IBD in murine models through the downregulation of inflammatory pathways, mitigation of oxidative stress, and modulation of fecal microbiota linked to bile acid metabolism [66]. Nevertheless, DMY shares the challenges common to many natural flavonoids, such as limited solubility, stability, and bioavailability, which impede its clinical translation and broader therapeutic application. To circumvent these challenges, Tang *et al.* developed a series of novel DMY-based nanoassemblies (DMY 1000 NAs) through the self-assembly of DMY with PEG₁₀₀₀ in aqueous medium. The resulting nanostructures displayed enhanced colloidal stability within the GI tract, coupled with superior biocompatibility and minimal systemic toxicity. Owing to the maximum retention of the phenolic hydroxyl group in the DMY molecule, the negatively charged DMY 1000 NAs were capable of targeting and adhering to colonic lesions, thereby exerting their potent antioxidant effects [148]. In murine models of CD and UC, DMY 1000 NAs have shown remarkable therapeutic efficacy. Notably, the study revealed that several other hydrophobic flavonoids could be formulated into analogous nanostructures, underscoring the broad applicability of this innovative approach.

4.2. Natural active compounds-based binary nanoassemblies

Hesperetin (HST), a flavonoid compound abundant in citrus fruits, is renowned for its exceptional anti-inflammatory and antioxidant properties [162]. Gao *et al.* used HST and BBR to self-assemble through electrostatic interaction, π - π stacking and hydrogen bonding to form binary carrier-free nanoparticles for synergistic treatment of IBD. The BBR-HST NPs demonstrated therapeutic efficacy in murine models of UC by mitigating inflammation, curbing the hyperactivation of immune cells, reconstituting the compromised intestinal mucosal barrier, and modulating the intestinal microbiome [149].

The rhubarb polysaccharide (DHP) is a bioactive component extracted from the rhizome of *Rheum* plants (*Rheum* spp.) with significant antioxidant, anti-inflammatory and immunomodulatory activities. Utilizing the inherent hydrophilic sugar moieties and the abundance of hydroxyl groups present in the structure of DHP, Feng *et al.* engineered a carrier-free nanoparticle formulation through coassembly with BBR via hydrophobic interactions and hydrogen bonding. The experimental outcomes revealed that DHP-BBR nanoparticles could adhere selectively to inflamed colon tissues, effectively mitigate the clinical signs associated with DSS-

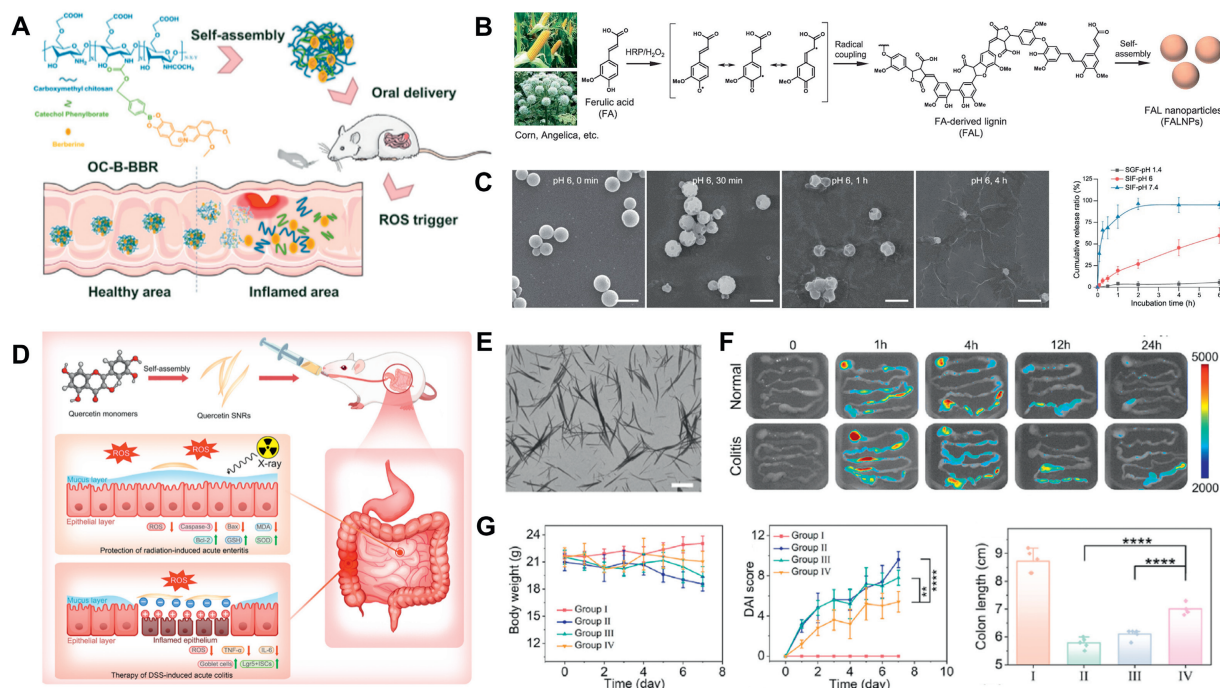


Fig. 3. Single natural active compounds-based nanoassemblies. (A) ROS-sensitive berberine prodrug self-assembling nanoparticles ameliorate UC and reshape gut microbiota in mice. (B) Schematic illustration of the preparation of ferulic acid-derived lignin nanoparticles (FALNPs). (C) Transmission electron microscope images of FALNPs incubated at pH 6 for different time intervals, and release rate analysis of cyclosporin A from the FAL@CSA in the media of simulated gastric liquid (SGF; pH 1.4) and simulated intestinal liquid (SIF; pH 6 or 7.4). Scale bar: 1 μ m. (D) Schematic illustration of the preparation process of quercetin SNRs and their protective effect for radiation-induced acute enteritis and therapeutic efficacy for DSS-induced acute colitis. (E) Transmission electron microscope image of quercetin supramolecular nanoribbons. Scale bar: 5 μ m. (F) Fluorescent images of GI tract in healthy and colitis mice after oral administration of quercetin SNRs at different time points. (G) Body weight change, clinical DAI score change and colon lengths of mice under different treatments. Data represent mean $\pm$ SDs ($n = 5$) (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$). (A) Reproduced with permission [147]. Copyright 2021, The authors, Frontiers Media S.A. (B, C) Reproduced with permission [40]. Copyright 2023 American Chemical Society. (D-G) Reproduced with permission [41]. Copyright 2023, Elsevier.

induced colitis in mice models, facilitate the restoration of the intestinal mucosal barrier, and promote an increase in the population of intestinal probiotics [163].

Feng *et al.* prepared a safe and macrophage-targeted oral drug delivery platform for UC treatment by self-assembling BBR and EGCG into nanoparticles, which were subsequently encapsulated within yeast microcapsules. The resulting BBR/MPN@YM formulation was capable of targeted drug delivery by selectively engaging with the Dectin-1 receptor on macrophages via the β -1,3-D-glucan moieties presented on the surface of the yeast microcapsules [164]. In comparison with the combination of BBR+EGCG or BBR/MPN NPs, BBR/MPN@YM demonstrated superior efficacy in mitigating colitis symptoms (such as reducing DAI score, restoring body weight and colon length), suggesting its potential as an efficacious therapeutic strategy for IBD.

Tannic acid (TA) is a naturally occurring and structurally complex polyphenol that is widely distributed in plants, especially in the bark, fruit, and leaves of various species. Due to the presence of multiple galloyl groups within its molecular structure, it frequently serves as a natural anti-inflammatory and antimicrobial crosslinking agent for a wide array of biomedical applications [165,166]. In one study, Chen *et al.* revealed that BBR and TA could autonomously self-assemble into nanoparticles through hydrogen bonding and π - π stacking interactions (Fig. 4A). The nanoparticles were subsequently functionalized with HA to facilitate active targeting of CD44 receptors, thereby augmenting their colon-specific homing capabilities [42]. As expected, HA-modified TA-BBR nanoparticles demonstrated an enhanced propensity for uptake and accumulation by colonic macrophages. In DSS-induced mouse model of colitis, HA-modified TA-BBR nanoparticles exhibited therapeutic efficacy by significantly mitigating colonic inflam-

matory cytokines and oxidative stress markers, reinforcing epithelial barrier function, and promoting the stabilization of the gut microbiome (Fig. 4B).

Overall, compared to traditional carrier-based NDDS, natural active compounds-based nanoassemblies eliminate the need for intricate carrier design and synthesis, streamlining formulation steps and avoiding potential carrier-related toxicity, which is more conducive to large-scale production and clinical translation. Notably, natural active compounds-based nanoassemblies often can offer higher drug payload capacities, even up to 100% drug loading [41]. Despite their advantages in treating IBD, there are still some obstacles that may impede their clinical translation. Firstly, a standardized preparation process should be established to achieve large-scale industrial production. Additionally, a thorough understanding of the assembly mechanisms is necessary to optimize characterization parameters and drug delivery properties. In particular, for the co-assembly of two drugs, determining the optimal ratio is crucial for achieving the best synergistic therapeutic effect [167]. Notably, precisely controlling drug release at the target site remains a challenge. Therefore, incorporating bioresponsive elements into the assembly or modifying the surface with targeting materials could be a promising strategy.

5. Phyto-derived nanostructures in the treatment of IBD

5.1. Phyto-derived NVs in the treatment of IBD

Plant-derived exosome-like nanovesicles (PELVs) are a class of biocompatible and biodegradable nanosystems. They are mainly vesicle structures composed of phospholipid bilayer, containing lipids, proteins, nucleic acids, and an arsenal of bioactive com-

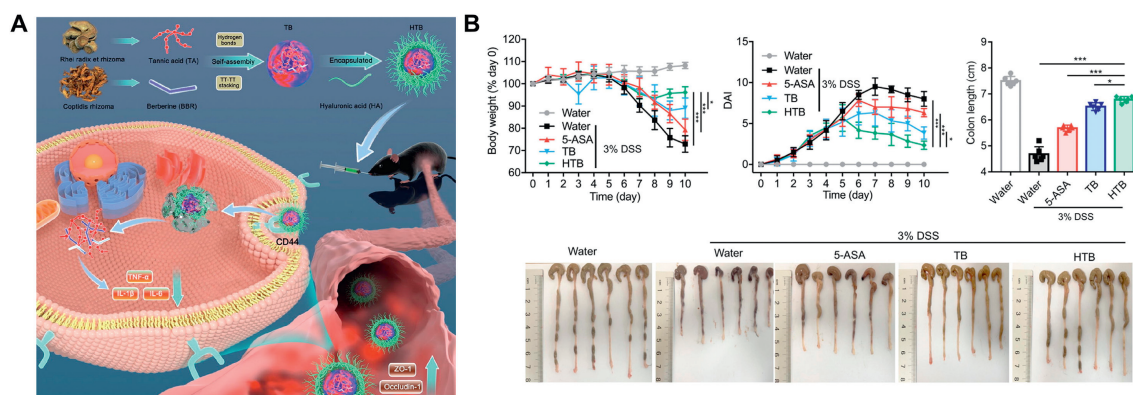


Fig. 4. Natural active compounds-based binary nanoassemblies. (A) Schematic illustration of BBR/tannic acid nanoassemblies for the treatment of UC. (B) Daily changes in body weight, DAI score, and colon length in DSS-induced colitis mice after oral administration of different formulations. Data are expressed as mean $\pm$ SD ($n=6$). * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. (A, B) Reproduced with permission [42]. Copyright 2022, Elsevier.

pounds. This composition grants PELNs a wide range of biological functions and therapeutic potential for treating various diseases [46]. Currently, PELNs have been successfully isolated from a variety of plants, including common edible plants such as ginseng, ginger, and broccoli [168]. These plants are readily accessible and predominantly edible, ensuring minimal adverse effects and low immunogenicity of PELNs. Common extraction methods include pretreating plant tissues *via* tissue lysis and tissue infiltration centrifugation, followed by separation and purification using techniques such as density gradient ultracentrifugation and ultrafiltration [169]. Notably, Researchers have developed a novel drug-delivery system using lipids derived from PELN (PELN lipid-derived nanovesicles, PLNVs) [170]. This system can deliver chemotherapy drugs, siRNA, DNA expression vectors, and proteins to various cell types, enhancing the efficacy of chemotherapy in inhibiting tumor growth, and thus represents a promising tool for drug delivery.

Several edible phyto-derived NVs have pointed the remarkable potential in the treatment and prevention of IBD [171–175]. In addition to their direct application as therapeutic agents, phyto-derived NVs also provide an excellent platform for drug delivery, phyto-derived NVs have also been reported to be capable of encapsulating small molecule compounds [176], siRNA [177], antibodies [173], and CRISPR-Cas9 for the treatment of IBD [178]. Notably, a clinical study is evaluating the safety and tolerability of ginger-derived exosomes alone or in combination with CUR in patients with IBD and the effect on symptoms and disease scores in patients with refractory IBD (ClinicalTrials.gov: NCT04879810). Therefore, phyto-derived NVs hold great promise for the treatment of IBD. The following sections describe in detail the emerging phyto-derived NVs in IBD therapy, as listed in Table S3 (Supporting information).

5.1.1. Phyto-derived NVs as therapeutic agents

As early as 2013, a pioneering study revealed the potential therapeutic effects of grape-derived exosome-like nanoparticles (GELNs) on IBD [179]. This investigation has elucidated that GELNs could traverse the intestinal mucosal barrier to specifically target intestinal stem cells and significantly promote the proliferation of *Lgr5^{hi}* intestinal stem cells through the Wnt/ β -catenin pathway, thereby remodeling intestinal tissue to play a pivotal role in the treatment of UC.

Ginger, the root of *Zingiber officinale*, is widely used in foods, fragrances and traditional medicines due to its beneficial properties such as aroma, nutrition and pharmacological activity [180]. Ginger and its main active ingredients 6-shogaol, zingerone, and 8-shogaol have demonstrated the potential to mitigate IBD *via* anti-inflammatory, antioxidant, and other mechanisms [181–183].

Professor Didier Merlin's research Group isolated a specific group of nanoparticles (GDNPs 2) from ginger, containing a high level of lipids, a small amount of protein, about 125 microRNAs and significant amounts of biologically active components such as 6-gingerol and 6-gingerol [45]. Further experimentation corroborated that GDNPs 2 had good safety and stability, and could be preferential uptake by intestinal epithelial cells and macrophages. Owing to the robust anti-inflammatory attributes and capacity to restore the integrity of the intestinal mucosal barrier, GDNPs 2 demonstrated exceptional therapeutic efficacy in combating both acute and chronic colitis, as well as colitis-associated cancer. Notably, Teng *et al.* revealed that microRNAs present within ginger-derived exosome-like nanoparticles possessed the capability to target *Lactobacillus rhamnosus* within the gut microbiome, leading to an increased production of indole-3-formaldehyde and the consequent induction of IL-22. This discovery underscored the potential of ginger-derived exosome-like nanoparticles to ameliorate colitis in mice by modulating the intestinal microbiota and fortifying the intestinal mucosal barrier through an IL-22-mediated pathway [44].

Turmeric (*Curcuma longa* L.) is a traditional Chinese herbal medicine with various biological activities, such as anti-inflammatory, anti-tumor, and hypolipidemic effects [184]. In addition, turmeric is edible, inexpensive and available in large quantities suggesting that turmeric derived NVs (TNVs) may be suggested as a novel drug for the treatment of multiple diseases. Gao *et al.* found that TNVs could accumulate in inflammatory sites of colon and exert excellent anti-inflammatory effect [171]. Furthermore, these TNVs facilitated the repolarization of M1 macrophages to the M2 phenotype, bolstering the repair of the compromised intestinal epithelial barrier and consequently alleviating the manifestations of colitis. In another study, Liu *et al.* isolated and purified a specific population of turmeric derived nanoparticles (TDNPs 2) by ultrafiltration and sucrose gradient centrifugation [185]. Ensuing *in vivo* experiments demonstrated that oral administration of TDNPs 2 facilitated its accumulation within the inflamed colonic tissues, mitigating colitis in murine models through the suppression of the NF- κ B signaling pathway and the enhancement of antioxidant gene HO-1 expression (Fig. 5A).

Tea is one of the most popular drinks in the world and has various beneficial effects on human health, including anti-inflammatory, antioxidant, blood lipid-lowering, Alzheimer's disease prevention, and immune-boosting properties. Additionally, active ingredients such as EGCG, epicatechin gallate, and tea polysaccharides have been found to exhibit anti-inflammatory effects, relieve oxidative stress, and regulate gut microbiota, thereby demonstrating potential in the prevention and treatment of IBD [188–190]. Consequently, the development of nanomedicines derived

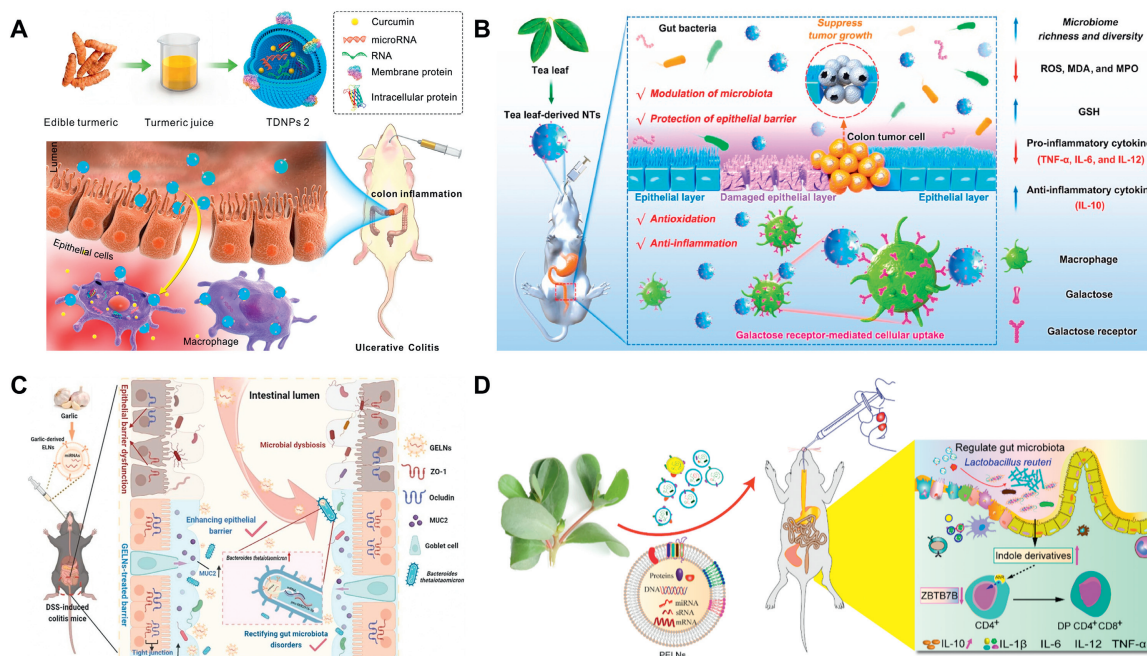


Fig. 5. Phyto-derived NVs as therapeutic agents for the treatment of IBD. (A) Turmeric-derived exosome-like nanovesicles with anti-inflammatory and pro-resolving bioactions for murine colitis therapy. (B) Schematic illustration of the preventive and therapeutic effects of oral tea leaf-derived natural NTs on IBD and its associated CAC. (C) peu-MIR2916-p3-enriched garlic exosomes ameliorate murine colitis by reshaping gut microbiota, especially by boosting the anti-colitic *Bacteroides thetaiotaomicron*. (D) Schematic illustration of therapeutic effects of oral *Portulaca oleracea*-derived natural exosome-like nanoparticles on UC. (A) Copied with permission [185]. Copyright 2022, The Authors, Springer Nature. (B) Copied with permission [172]. Copyright 2021, Elsevier. (C) Copied with permission [186]. Copyright 2024, Elsevier. (D) Copied with permission [187]. Copyright 2023, The Authors, Springer Nature.

from tea for the treatment of IBD represents an exciting therapeutic approach. Zu *et al.* developed a collection of tea leaves-derived exosome-like nanotherapeutics (NTs) that are abundant in lipids, functional proteins, and bioactive small molecules [172]. Notably, due to the presence of surface galactose groups, these NTs facilitated targeted delivery to macrophages via galactose receptor-mediated endocytosis, thereby achieving high cellular internalization efficiency. Oral administration of these NTs exhibited preventive and mitigating effects on UC and colitis-associated colon cancer, acting through anti-inflammatory and antioxidant mechanisms, restoration of the colonic mucosal barrier, and modulation of the intestinal microbiota (Fig. 5B). Han *et al.* extracted nanoparticles encapsulating caffeine, EGCG, gallic acid, and epicatechin gallate from the soaking liquid of black tea [191]. Oral administration of black tea-derived nanoparticles in the intestine restored the integrity of intercellular tight junction, inhibited inflammatory infiltration and alleviated UC.

Garlic (*Allium sativum* L.) is a ubiquitous culinary herb. Beyond the role as a seasoning agent, it has been widely esteemed in traditional medicine for its antimicrobial, anti-inflammatory, and cardioprotective attributes [192]. Wang *et al.* discovered that Garlic-derived exosome-like nanoparticles (ELNs), enriched with functional proteins and microRNAs, effectively mitigated DSS-induced colitis (Fig. 5C). This therapeutic effect was achieved through the uptake of Garlic-derived ELNs by intestinal microorganisms, which subsequently modulated inflammation, restored the mucosal barrier, and restructured the gut microbiota [186]. Mechanistically, a specific microRNA within the GELNs, peu-MIR2916-p3, selectively enhanced the proliferation of *Bacteroides thetaiotaomicron* (a commensal bacterium recognized for its beneficial role in ameliorating colitis symptoms).

Portulaca oleracea L. is a medicinal herb with anti-inflammatory, antioxidant and immunomodulatory activities that has demonstrated benefits in IBD [193,194]. Zhu *et al.* discovered that *Portulaca oleracea* L-derived exosome-like nanoparticles (PELNs) of-

fered comparable protection against DSS-induced colitis in mice, as well as in IL-10 deficient murine models of colitis (Fig. 5D). Research has shown that PELNs possessed outstanding safety profiles and gastrointestinal stability, with the capacity to selectively target the inflamed regions of the colon [187]. The therapeutic impact of PELNs is associated with its capacity to stimulate the expansion of double-positive CD4⁺CD8⁺ T cells via the *Lactobacillus reuteri*-derived indole/AhR/Zbtb7b axis.

Furthermore, NVs derived from certain plants, such as hemp, sweet oranges, mulberry, broccoli, lycium barbarum, pueraria lobate, ginseng, cabbage, aloe and momordica charantia, have also exhibited excellent therapeutic effects against IBD (Supporting information).

5.1.2. Phyto-derived NVs as delivery vectors

The phospholipid bilayer architecture of phyto-derived NVs endows them with the capability to entrap therapeutic molecules, while providing robust gastrointestinal stability to safeguard the encapsulated agents from degradation. Remarkably, as phyto-derived NVs are harvested from natural sources, they typically exhibit enhanced gastrointestinal stability and diminished immunogenicity when compared to the synthetic counterparts, which facilitates diminished *in vivo* clearance and immune responses, enhancing the efficacy of drug transport [195,196]. Consequently, plant-derived NVs are regarded a promising alternative for advanced drug delivery systems.

Grapefruit is a widely-consumed fruit that offers significant nutritional benefits. Its primary active ingredient, naringin, has been found to have a positive impact on experimental colitis by regulating the levels of inflammatory cytokines and reducing oxidative stress [197]. Besides, naringenin, a hydrolytic product of naringin, has been reported to provide protection against experimental colitis by inhibiting the TLR4/NF-κB signaling pathway [198]. An investigation elucidated that grapefruit-derived NVs (GDNs) could protect against DSS-induced colitis in mice by targeting intestinal

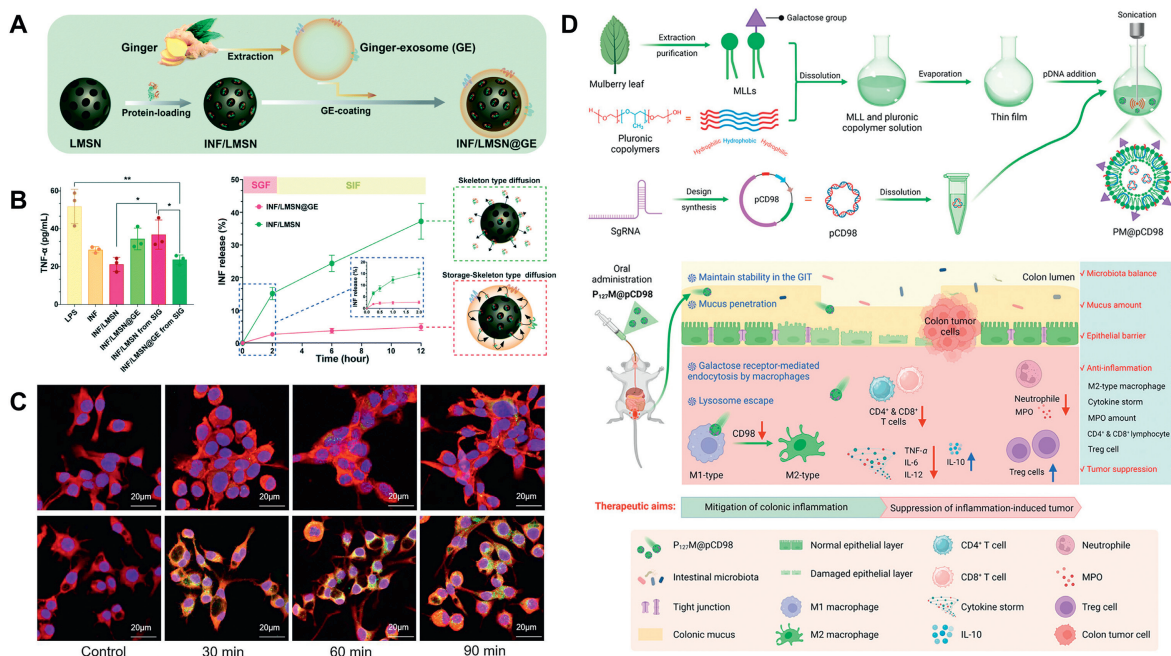


Fig. 6. Phyto-derived NVs as delivery vectors for the treatment of IBD. (A) Schematic illustration of ginger-derived exosome and an inorganic framework for high-performance delivery of oral antibodies. (B) TNF- α level in the culture supernatant of RAW264.7 cells treated with different preparations of simulated gastric fluid (left), and *in vitro* release profiles of INF/LMSN and INF/LMSN@GE in the simulated gastric fluid and imulated intestinal fluid (right). Data are means $\pm$ SD ($n = 3$). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (C) Fluorescence images of the internalization of 6-gingerol-load ginger-derived natural-lipid nanoparticle by CT-26 (above) and Raw 264.7 cells (below) at different time points. Lipid nanoparticle-DIO (green channel), nucleus-DAPI (blue channel), cytoskeleton-TRITC (red channel). (D) Schematic illustration of Mulberry Leaf-derived lipid nanoparticles for targeted delivery of CRISPR/Cas9 for mitigation of colonic diseases. (A, B) Reproduced with permission [173]. Copyright 2021 Royal Society of Chemistry. (C) Reproduced with permission [176]. Copyright 2020, Elsevier. (D) Copied with permission [178]. Copyright 2024, John Wiley & Sons.

macrophages and up-regulating HO-1 level and down-regulating IL-1 β and TNF- α expression [174]. The therapeutic efficacy of GDNs are, in part, attributed to their compositional richness in phosphatidylethanolamine, phosphatidylcholine, and naringin, which are endowed with antioxidant and anti-inflammatory attributes. Interestingly, leveraging the inherent biocompatibility and biodegradability of GDNs, coupled with high gastrointestinal stability and targeted binding to intestinal macrophages, the anti-inflammatory drug methotrexate was encapsulated within GDNs for synergistic and integrated drug delivery. This approach significantly reduced the toxicity of MTX and substantially enhanced its therapeutic efficacy in treating DSS-induced colitis in mice, compared to free MTX. These findings indicated that phyto-derived NVs can serve dual roles: As therapeutic agents and as oral delivery platforms for drugs, enabling a synergistic approach to the treatment of IBD.

Zhang *et al.* discovered that ginger-derived nanolipids could efficiently encapsulate siRNA-CD98 with a high encapsulation efficiency of $61\% \pm 8\%$. Compared to siRNA-CD98 alone, the ginger-derived lipid vesicles loaded with siRNA-CD98 exhibited targeted delivery to colonic epithelial cells and macrophages, significantly suppressing CD98 mRNA expression in the colon [177]. Interestingly, Mao *et al.* constructed a biomimetic nanocomposite (INF/LMSN@GE) for oral delivery of anti-TNF- α antibodies infliximab utilizing ginger-derived exosomes and large-mesoporous silicon nanoparticles (LMSNs) (Fig. 6A). This integration of LMSNs elegantly addressed the limitations associated with low drug loading capacity and the inherent stability issues of exosomes. The GE confers upon INF the capacity to withstand the acidic environment and enzymatic digestion of the GI tract, enabling rapid release in the colon (Fig. 6B). Moreover, the INF/LMSN@GE nanocomposite demonstrated exceptional colon-specific targeting, and efficient intestinal epithelial permeability. In DSS-induced murine model of colitis, oral administration of INF/LMSN@GE effectively inhibited

NLRP3 inflammasomes and produced significant anti-inflammatory effects, surpassing the therapeutic outcomes achieved through intravenous administration [173]. In another investigation, Yang *et al.* discovered that ginger-derived natural-lipid (NL) nanoparticle could serve as an exceptional delivery platform, facilitating the targeted transport of 6-gingerol to inflamed locations within the colon [176]. Experimental results demonstrate that 6-gingerol-load NL exhibited a delayed drug release profile and could be effectively internalized by both CT-26 and Raw 264.7 cells (Fig. 6C). In the DSS-induced murine model of colitis, oral administration of 6-gingerol-load NL resulted in a significant reduction in inflammatory markers and expedited wound healing processes.

In recent years, the CRISPR/Cas9 system has emerged as a formidable gene-editing tool with applications spanning basic research and prospective medical interventions [199,200]. Nevertheless, the efficacious oral delivery of the CRISPR/Cas9 machinery remains a formidable challenge to be surmounted. In one study, Ma *et al.* used mulberry leaf-derived lipid nanoparticles (LNP) to deliver CRISPR/Cas9 plasmid for CD 98 knockdown, and incorporated Pluronic F127 to further improve the gastrointestinal stability and mucus barrier permeability of LNP [178]. The resulting P127M@pCD98 nanocomplexes were capable of actively targeting colonic epithelial cells and macrophages *via* surface-exposed galactose terminal groups, thus improving cellular uptake, with a transfection efficiency of 2.2-fold over Lipofectamine 6000 (a novel efficient gene transfection reagent). Notably, oral administration of P127M@pCD98 significantly downregulated CD98 expression, reduced inflammatory responses, repaired the colonic barrier, and reconstituted the gut microbiota. In murine models of UC and CAC, P127M@pCD98 demonstrated robust therapeutic efficacy, confirming the feasibility and effectiveness of using mulberry leaf-derived LNPs as an oral CRISPR/Cas9 delivery platform (Fig. 6D).

In summary, phyto-derived NVs hold significant promise as natural therapeutic agents and drug delivery vehicles in the treatment

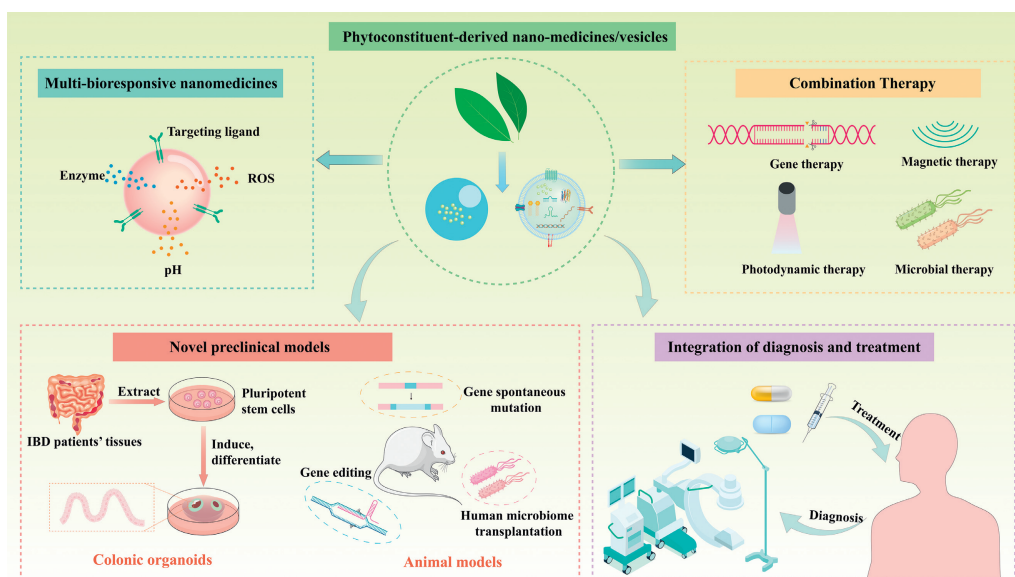


Fig. 7. Schematic diagram of future directions for phytoconstituent-derived nano-medicines/vesicles.

of IBD. Unlike mammalian-derived exosomes, phyto-derived NVs contain a variety of secondary metabolites unique to plants, such as grapefruit-derived NVs containing naringin and naringenin, and ginger-derived NVs detectable for 6-shogaol [174,201,202]. These components impart distinct bioactivities to phyto-derived NVs, highlighting their potential in drug delivery and disease treatment. However, like mammalian-derived exosomes, yield and purity are crucial for the clinical application of phyto-derived NVs. Furthermore, the consistency of NVs from different batches, regions, and seasonal variations of plants requires thorough evaluation. More clinical trials are also necessary to determine the *in vivo* fate and safety of phyto-derived NVs.

5.2. Phyto-derived other nanomedicines

Apart from phyto-derived NVs, other nanoscale structures have also been identified in some plants (Supporting information).

6. The possible future directions of phytoconstituent-derived nano-medicines/vesicles

Despite significant advancements, the clinical application of these nano-medicines/vesicles is not without challenges. Consequently, we will delve into the current quandaries faced by these nano-medicines/vesicles and explore potential future directions (Fig. 7).

- (1) The development of phytoconstituent-derived multi-bioresponsive nano-medicines/vesicles can provide strong support for precision treatment of IBD. Patients with IBD experience multiple environmental changes, such as changes in colon pH, transit time, intestinal pressure, and permeability, which render single stimulus-response NDDSs inadequate for practical application [203]. Therefore, the development of NDDSs with multi-responsive characteristics holds immense potential for optimizing drug delivery to specific sites and substantially minimizing deleterious side effects. At present, some researchers have developed NDDSs with multiple biological responses of pH/Redox/active targeting, which demonstrated highly efficient targeted delivery, on-demand release, and superior therapeutic efficacy [135,136,138].
- (2) Developing phytoconstituent-derived nanodots for the treatment of IBD. In recent years, nanodots have emerged as a

novel biomaterial and have been employed in the diagnosis and treatment of various diseases [204]. Yang *et al.* discovered that by simply heating a solution of natural polyphenol monomers, they can undergo physical assembly and oxidative polymerization to form nanodots with particle sizes ranging of 3–12 nm. These nanodots exhibited excellent biocompatibility, could cross the blood-brain barrier and extend circulation time, demonstrating promising therapeutic effects on Alzheimer's disease [205]. Furthermore, Li *et al.* discovered that black tea-derived nanodots could eradicate H1N1-methicillin-resistant *Staphylococcus aureus* pneumonia and quell cytokine storms by blocking active sites on H1N1 and trans-membrane interactions with methicillin-resistant *Staphylococcus aureus* [206]. These phytoconstituent-derived nanodots with simple fabrication process, high biocompatibility and definite therapeutic effect may provide a new direction for the treatment of IBD.

- (3) Exploring the combined use of phytoconstituent-derived nano-medicines/vesicles with other therapeutic approaches. In order to improve the therapeutic effects and reduce the side effects of drugs, there is growing interest in exploring the combined use of phytoconstituent-derived nano-medicines/vesicles with other therapeutic approaches, such as gene therapy, photodynamic therapy, magnetic therapy and microbial therapy. For example, siCD98-loaded CUR nanoparticles and ginger-derived exosomes have been shown to exert combined effects on UC by protecting the mucosal layer and reducing inflammation both *in vitro* and *in vivo* [177,207]. Photodynamic therapy, which is a novel therapeutic method with few side effects, repeatable manipulation, controllability and specificity, has shown potential for the treatment of IBD. A study reported that low-dose photodynamic therapy combined with liposomal formulation (namely Foslip) could alleviate colitis and prevent colitis-associated cancer by reducing the expression of various inflammatory mediators, regulating gut microbiota and reducing neutrophil influx [208]. Moreover, the magnetism of magnetic therapy may help to increase the residence time of magnetic nanoparticles in the part of interest in the colon for targeted drug delivery to treat IBD [209]. Notably, considering the important role of gut microbiota in the pathogenesis of IBD, phytoconstituents combined with microbial therapy provides a broad platform for the treatment of IBD. Previous studies have shown that some phytocon-

- stituents such as CUR, Res can reshape the gut microbiome and alleviate IBD symptoms [210,211]. Nanotechnology-based microbial therapies give bacteria the ability to effectively and precisely control activity and biological behavior, as well as edit treatment patterns carrying different cargo molecules, including small molecules of drugs, proteins and genes [212,213]. Furthermore, bacteria-derived outer membrane vesicles have shown beneficial anti-inflammatory, immunomodulatory, and mucosal barrier protective effects in colitis models [10,214,215], as well as the capability with cargo loading [216]. Therefore, the combination of phytoconstituent-derived nano-medicines/vesicles and other therapies will open up entirely new modalities of the treatment of IBD.
- (4) The establishment of novel preclinical model of IBD is essential for comprehending the pathological mechanisms of the disease and validating the effectiveness of phytoconstituent-derived nano-medicines/vesicles prior to clinical trials. Although there are some immunological and histopathological similarities between chemical-induced IBD models commonly used in current experimental studies and phenotypes of IBD patients, there are some limitations. As the pathogenesis of IBD is a complex process involving multiple factors, a single chemical induction model is difficult to simulate the actual situation, for example, the model cannot reflect the role of abnormal immune system, dysmicrobial flora and other factors in the disease. Furthermore, the short half-life of chemicals limits the duration of the model, thereby failing to accurately replicate the onset and progression of chronic enteritis. Therefore, there is an urgent need to develop new IBD models. Colonic organoids are *in vitro* three-dimensional culture models that involve the isolation of stem cells from a patient's colonic tissue and their subsequent cultivation under specific conditions to develop structures akin to miniaturized colonic architectures [217]. Colonic organoids offer a robust platform for investigating IBD, due to their close resemblance to the physiological conditions of IBD patients, they are well-suited for applications in drug discovery, toxicity assessments, and personalized medicine initiatives [217–221]. In recent years, researchers have established more representative and sustainable IBD animal models through employing advanced gene editing technology, spontaneous mutation and human microbiome transplantation, such as IL-6/IL-10 double-deficient mice (more pronounced gut inflammation and earlier disease onset) [222], mucin 1 knockout mice (more severe intestinal inflammation and damage) [223], I-kappa-B kinase gamma knockout mice (serious chronic intestinal inflammation and immune disorders) [224], T-cell adoptive transfer model (allowing researchers to explore the specific role of T cells in triggering and maintaining intestinal inflammation and its mechanisms) [225], senescence accelerated mouse (SAM) strain SAMP1/YitFc (spontaneously develop similar human IBD intestinal inflammation and related symptoms) [226], and human microbiota-associated mouse model (allowing researchers to explore the interactions between the microbiome and the host, as well as their impact on IBD) [227]. These animal models better emulate the characteristics of human IBD and provide a more effective experimental platform for researchers.
- (5) The development of phytoconstituent-derived nano-medicines/vesicles based on the integration of IBD diagnosis and treatment has the potential to achieve early diagnosis, targeted positioning, and precise treatment of IBD. As a chronic disease, IBD requires continuous follow-up to monitor disease progression, treatment response, and remission. Currently, endoscopy and histopathological analysis are the common diagnostic procedures for IBD, but these techniques are invasive and may fail to detect cellular and molecular changes that occur in the body [228,229]. Therefore, biomarkers-related imaging is rapidly being developed for the integration of diagnosis and treatment of IBD. MPO can catalyze the production of toxic substances, promote inflammatory reactions, and cause tissue oxidative damage [230]. Studies have shown that the expression of MPO in IBD is positively correlated with the degree of IBD disease activity, which can be used as a clinical indicator of IBD disease activity [231,232]. Yan *et al.* designed an integrated polymer-based nanodiagnosis and treatment platform by incorporating natural compounds Res and betulinic acid (BA) and two lipophilic dyes DiL and DiD into nanoparticles (DiL/DiD-BA/Res@NPs) [233]. DiL/DiD-BA/Res@NPs could target BA and Res delivery to the inflammatory sites in the colon to exert synergistic anti-inflammatory effects. Notably, when the small molecule fluorescent probe luminol is injected intravenously, it detected MPO at the site of colonic inflammation and transferred the emitted light to the highly aggregated DiL/DiD-loaded BA/Res@NPs, thus enabling highly sensitive bioluminescence imaging of colitis tissue for precise detection of UC. In another study, Zeng *et al.* designed a pH/ROS dual-response nanosystem for the detection and treatment of UC [234]. The outer enteric-coated coating releases the chromophore-borate-DMY prodrug in response to the pH of the colonic site. Subsequently, the prodrug was released in response to a high concentration of ROS in the colon to treat UC, and chromophores were released for near-infrared second-window fluorescence and photoacoustic imaging for UC diagnosis and recovery evaluation.
- (6) The process of clinical translation of phytoconstituent-derived nano-medicines/vesicles should be accelerated. While phytoconstituent-derived nano-medicines/vesicles have shown great potential for treating IBD at the preclinical stage, there are few successful stories of clinical application. First, the lack of unified preparation methods, limitations of the characterization methods and the inability of industrial production are significant challenges for phytoconstituent-derived nano-medicines/vesicles [235]. Therefore, it is essential to optimize and tightly control the manufacturing processes of phytoconstituent-derived nano-medicines/vesicles that comply with chemistry, manufacturing and control, and good manufacturing practices. Besides, there are uncertainties in the distribution and metabolism of phytoconstituent-derived nano-medicines/vesicles. The distribution and metabolism of phytoconstituent-derived nano-medicines/vesicles *in vivo* are often affected by many factors, such as physiological environment, physicochemical characteristics of drugs and drug delivery mode. These factors may lead to uncertainties in the efficacy and safety of phytoconstituent-derived nano-medicines/vesicles. Future research should focus on strengthening clinical studies of phytoconstituent-derived nano-medicines/vesicles to verify their biosafety and efficacy and promote their use in clinical practice.

7. Conclusions

In summary, phytoconstituent-derived nano-medicines/vesicles offer a promising approach to enhance the efficacy and safety of therapeutic interventions, particularly for challenging diseases like IBD, by combining the intrinsic properties of natural compounds with the advanced capabilities of nanotechnology. With further rational design and more clinical validation, phytoconstituent-derived nano-medicines/vesicles are poised to become potent weapons against IBD in the near future.

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.

CRediT authorship contribution statement

Linzhou Yin: Writing – original draft. **Xiaowen Jiang:** Writing – original draft. **Miao Wang:** Conceptualization. **Yiren Yang:** Conceptualization. **Zhonggui He:** Supervision. **Jin Sun:** Writing – review & editing. **Huiyuan Gao:** Writing – review & editing. **Mengchi Sun:** Writing – review & editing.

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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.2024.110224.

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