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Bioinspired and bioderived nanomedicine for inflammatory bowel disease

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Abstract

Due to its chronic nature and complex pathophysiology, inflammatory bowel disease (IBD) poses significant challenges for treatment. The long-term therapies for patients, often diagnosed between the ages of 20 and 40, call for innovative strategies to target inflammation, minimize systemic drug exposure, and improve patients' therapeutic outcomes. Among the plethora of strategies currently pursued, bioinspired and bioderived nano-based formulations have garnered interest for their safety and versatility in the management of IBD. Bioinspired nanomedicine can host and deliver not only small drug molecules but also biotherapeutics, be made gastroresistant and mucoadhesive or mucopenetrating and, for these reasons, are largely investigated for oral administration, while surprisingly less for rectal delivery, recommended first-line treatment approach for several IBD patients. The use of bioderived nanocarriers, mostly extracellular vesicles (EVs), endowed with unique homing abilities, is still in its infancy with respect to the arsenal of nanomedicine under investigation for IBD treatment. An emerging source of EVs suited for oral administration is ingesta, that is, plants or milk, thanks to their remarkable ability to resist the harsh environment of the upper gastrointestinal tract. Inspired by the unparalleled properties of natural biomaterials, sophisticated avenues for enhancing therapeutic efficacy and advancing precision medicine approaches in IBD care are taking shape, although bottlenecks arising either from the complexity of the nanomedicine designed or from the lack of a clear regulatory pathway still hinder a smooth and efficient translation to the clinics.

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KEYWORDS

biotherapeutics, extracellular vesicles, inflammatory bowel disease, nanomedicine, nanoparticles

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a complex multifactorial inflammatory chronic disorder of the gastrointestinal (GI) tract. Several elements have been identified as key players in the pathogenesis of this disease, such as genetic predisposition, environmental factors, gut microbiota, and an inappropriate immune response (Z. Cai, Wang, & Li, 2021). The two major forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD). The functional damage to the epithelium in active IBD leads to similar clinical manifestations for both disorders (diarrhea, vomiting, abdominal pain); nevertheless, the involved intestinal regions are different. CD can affect any part of the GI tract, but most commonly it affects the ileum and colon, and the inflammation features are typically transmural (Ananthakrishnan et al., 2022). In UC, extensive superficial mucosal ulceration develops, extending from the rectum to more proximal areas (Ananthakrishnan et al., 2022). These conditions result in debilitating physical and psychosocial symptoms which reduce dramatically the quality of life of patients, which are also at increased risk of developing colorectal cancer (Shah & Itzkowitz, 2022).

There is no effective known cure for IBD, and all treatment options can only help the patient to control the disease. Treatments include the use of medication, clinical trials, alterations in diet and nutrition, and sometimes surgical procedures to repair or remove affected portions of the GI tract. In general, the primary goals of clinical practice guidelines aim at inducing and maintaining clinical remission. In mild-to-moderate UC, topical and/or oral aminosalicylates are recommended for the induction and maintenance of remission. Other pharmacological options include topical and oral corticosteroids, and thiopurines (Gros & Kaplan, 2023; Raine et al., 2022). In moderate-to-severe UC, oral corticosteroids are used for induction of remission although they are not recommended as maintenance therapy due to a lack of long-term efficacy and strong adverse effects (Gros & Kaplan, 2023). In case of non-responsiveness to corticosteroids, anti-TNF agents, such as infliximab (IFX) and adalimumab, are recommended for induction and maintenance of remission. Other treatment options include thiopurines, Janus kinase (JAK) inhibitors, such as tofacitinib, anti-integrins (monoclonal antibody anti-α4β7 integrin), and inhibitors of interleukin IL-12/IL-23 (Gros & Kaplan, 2023; Raine et al., 2022). Oral corticosteroids are used to induce clinical response and remission in CD and, in case of non-responsiveness, anti-TNF agents. For maintenance of remission different treatments—such as anti-TNF agents, anti-integrins, inhibitors of interleukin IL-12/IL-23, thiopurines, and methotrexate—may be used depending on the clinical history of the patient (Torres et al., 2020).

Both topical and systemic therapeutic approaches present limitations in managing this disease. Rectal formulations, besides being less accepted by patients due to the administration route, present limited reach in the colon and the patients might experience drug leakage and fecal urgency. Oral and parenteral therapies, on the other hand, are related to severe short and long-term adverse effects (Gros & Kaplan, 2023). In this scenario, nano-based therapies offer several advantages, including enhanced drug solubility and bioavailability, mucoadhesion and mucus-penetrating properties, controlled drug release, and targeted delivery, which results in reduced drug toxicity. The targeted delivery to injured tissues—and minimal exposure to the healthy ones—is provided by two mechanisms. The first one, passive targeting, relies on tuning the physical properties of the nanoparticle, such as size and surface charge, to promote drug accumulation in the inflamed tissue via the enhanced permeability and retention (EPR) effect or epithelial EPR (eEPR) effect (Dilliard & Siegwart, 2023; Gou et al., 2019; Lamprecht, 2010). The second one, active targeting, involves modifying the surface of the nanoparticles with chemical or biological moieties that specifically bind to receptors highly expressed by cells in the targeted organ or tissue (Dilliard & Siegwart, 2023). The advantages offered by nanoparticles can be expanded by the utilization of bioinspired and bioderived materials. This is because the biocompatible nature of these materials produces nanoparticles with enhanced capacity to cross biological barriers, reduced immunological stress and, thus, prolonged circulation times. Bioinspired nanomedicines are produced with materials of biological origin, such as biopolymers, lipids, and proteins, which can form the nanoparticle matrix or be utilized for surface functionalization. Bioderived nanomedicines, on the other hand, consist of components produced by animals, plants, or microbes that possess therapeutic effects or are employed for encapsulating and delivering drugs.

In the following sections, we will critically discuss advancements made in the past 5 years in the development of bioinspired and bioderived nano-based formulations for small molecules and biologics for the treatment of IBD and, finally, we will draw conclusions connecting overarching themes and highlighting gaps and research perspectives.

2 | BIOINSPIRED NANOMEDICINE FOR SMALL MOLECULES

The pharmacological management of IBD is typically initiated with small molecule-based therapies via rectal or oral administration. Parenteral drug formulations are administered in case of non-responsiveness to rectal and oral therapies. Rectal formulations often present poor mucoadhesion and mucopenetration, limiting their efficacy, while oral drug formulations may be susceptible to gastric pH and enzymatic degradation, resulting in reduced drug concentration in the inflamed colon. On the other hand, parenteral drug formulations lack colon-targeting properties and may induce off-target effects. These challenges can be addressed by the design of tailor-made nanocarriers. To this aim, nature provides a wide portfolio of components, such as polysaccharides, proteins, and lipids, which can be exploited to design customized delivery platforms with enhanced therapeutic outcomes. Compared to synthetic building blocks, their bioinspired nature endows the final nanomedicine with the ability to pass biological barriers more easily, improves its biocompatibility, bioavailability, biodegradability, and can provide specific targeting (Sabu et al., 2018). The bench-to-bedside translation of bioinspired nanomedicines can be though hampered by the reproducibility driven by the intrinsic batch-to-batch variability and source of biomolecules, the complexity of the delivery system, and the stability in physiological conditions (Z. Wang, Wang, et al., 2023).

In this section, we describe bioinspired nanomedicines for small molecules (natural and synthetic) that have recently showcased their potential for the treatment of IBD throughout the three major administration routes for GI pathologies, that is, oral, parenteral, and rectal. The main biopolymer-based and lipid-based nanocarriers discussed in this section are summarized in Figure 1a,b.

2.1 | Oral administration

The development of nanomedicines for IBD primarily focuses on oral formulations as this route offers the possibility of self-administration and flexibility in the dosage regimen, leads to high patient compliance, and reduced production costs, as it may avoid sterile production conditions needed for parenteral formulations (Andretto et al., 2021). Oral formulations need to overcome a series of barriers to effectively reach and deliver the drug at the colon site, and nanoparticles offer a broader level of flexibility and tunability than traditional oral dosage forms that could ensure protection of the therapeutic agent against the harsh acidic and enzymatic conditions in the stomach. Besides that, colon-targeted drug delivery can be achieved by modulating the composition of these systems including specific targeting moieties, thus promoting high drug concentration in the inflamed tissue and fewer systemic side effects. Bioinspired strategies for oral formulations capitalize on favorable properties of biopolymers, such as polysaccharides and proteins, and lipids, resulting in drug-loaded nanoparticles that can eventually be included in nanocomposites and nano-in-micro systems.

2.1.1 | Polymeric nanoparticles

Biopolymers represent attractive materials to prepare nanoparticles and nanocomposites for the delivery of therapeutic agents targeting IBD, in virtue of their excellent biocompatibility, biodegradability, abundance, stability, and possibility of degradation in the colon (Lima et al., 2021). Polysaccharides and their derivatives have been extensively exploited for this purpose, in particular chitosan, which is derived from the polymer chitin found in the exoskeletons of crustaceans and in the cell walls of some fungi. Its cationic nature provides strong mucosal attachment, making it an ideal carrier for colon-targeting delivery systems (Kulkarni et al., 2022). Most of the recent chitosan-based systems reviewed here were developed for the oral administration route, and the protection of the loaded drug against premature release in the gastric environment was typically achieved by including in the formulation polymers such as hydroxypropyl methylcellulose phthalate—also acting as a crosslinker for chitosan (Mahami et al., 2023), pectin (Ahmed et al., 2022) or Eudragit® S100 (Maleki et al., 2023; Mohanbhai et al., 2022). Alginate, a biopolymer derived from brown algae, also provides a certain degree of gastroresistance and modulation of the release profile. Alginate alone (Dong et al., 2021) or in combination with chitosan (Lei et al., 2023; S. Li, Jin, et al., 2021; L. Wang, Fu, et al., 2023) have been utilized for the production of colon-targeted nanoformulations. When alginate was used to coat trimethylchitosan nanoparticles loaded with low molecular weight heparin (indicated for its anti-inflammatory, anticoagulant and mucosal healing effects in UC), the premature release of the drug in the upper GI tract was hampered, and a sustained release in the colon was

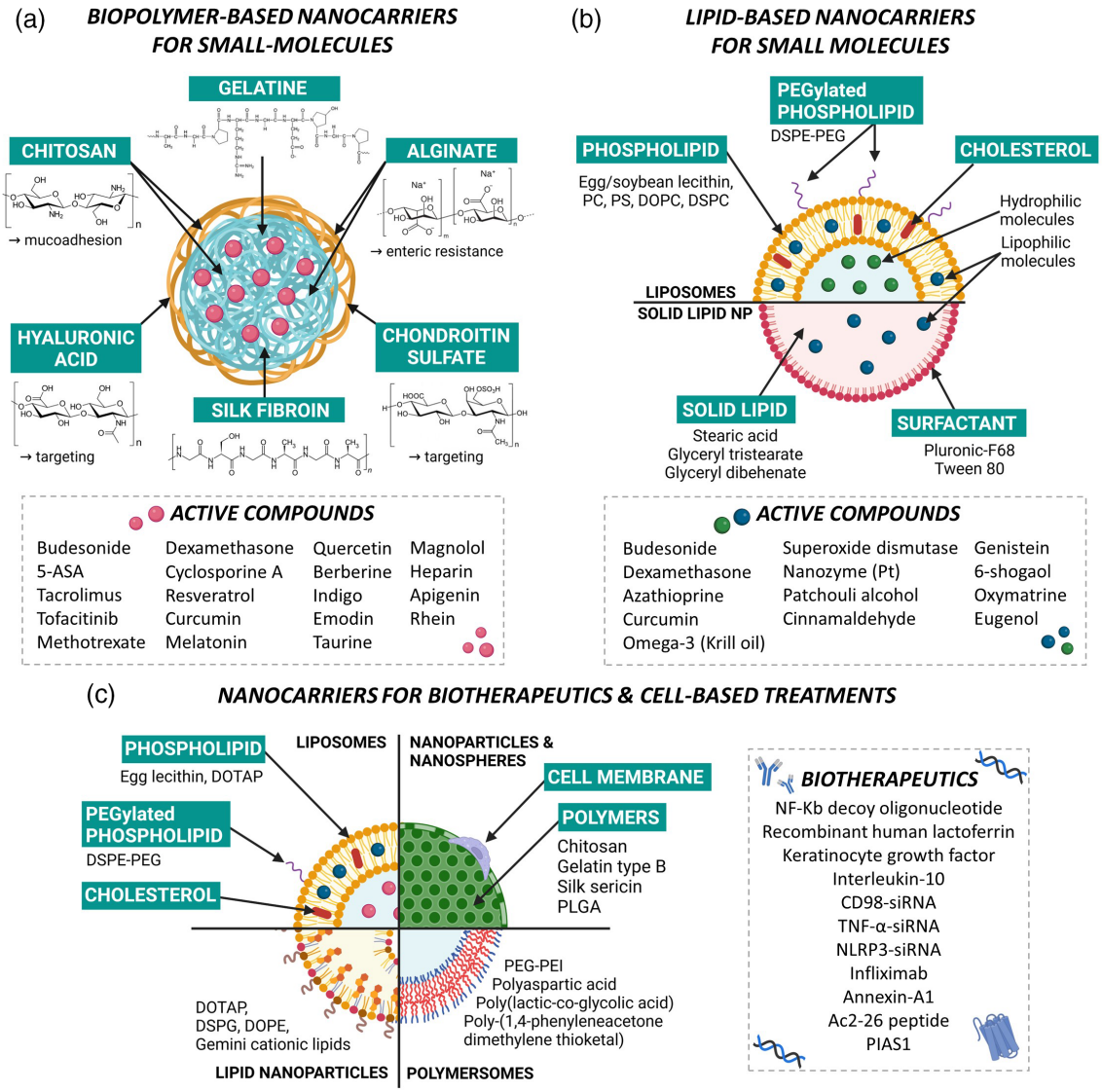

FIGURE 1 Bioinspired nanocarriers for IBD. (a) Representation of a polymeric nanoparticle, the main biopolymers reported for its production and the encapsulated small molecules. (b) Representation of a liposome (top) and a solid lipid nanoparticle (bottom), the main lipids reported for their production and the encapsulated small molecules. (c) Representation of a liposome (top-left), nanoparticles and nanospheres (top-right), lipid nanoparticles (bottom-left) and polymersomes (bottom-right), the main biopolymers and lipids utilized for their production and the encapsulated biotherapeutics.

achieved (Y. Yan et al., 2020); moreover, such alginate-coated nanoparticles demonstrated a lower oral absorption and stronger mucoadhesion, thus providing better colon-targeting property in the treatment of UC. The mucoadhesion property of these nanoparticles (NPs) was evaluated both ex vivo and in vivo. For the ex vivo assessment, NPs were incubated with colon tissues from normal and colitis mice, and kilo counts per second (kcps) values were evaluated by dynamic laser light scattering (DLS). For the in vivo assessment, normal and colitis mice were treated with FITC-loaded NPs. The fluorescence intensity in the colon tissues was then observed using confocal laser scanning microscopy. Chitosan and alginate were also used to prepare coatings using a layer-by-layer method, to obtain effective colon targeting of polymeric nanoparticles (Jin et al., 2021; X. Zhang, Yuan, Wu, et al., 2023) and drug nanocrystals (Oshi et al., 2020; N. Wang, Shao, et al., 2022). Oshi et al. demonstrated that this strategy allows for the accumulation of curcumin nanocrystals in inflamed tissues of the colon, minimizing drug release in the stomach and small intestine (Oshi et al., 2020). In a recent study by Zhang et al., a chitosan-alginate layer-by-layer was used to coat the surface of CO prodrug-loaded mesoporous polydopamine nanoparticles. This system is capable of releasing CO in the oxidative microenvironment of the inflamed colon, and, in IBD-induced

mice models, it effectively reverses the pro-inflammatory microenvironment and restores gut barrier functions through multiple mechanisms (X. Zhang, Yuan, Wu, et al., 2023).

The accumulation of the nanoparticles in the site of interest could alternatively be achieved through active targeting strategies. Chitosan-modified curcumin-loaded nanoparticles were used to develop a nanotherapeutic based on the active targeting of CD44, a transmembrane glycoprotein that is over-expressed on the surface of colon epithelial cells and macrophages in UC tissues (X. Zhang et al., 2019). The particles were functionalized either with the biopolymer chondroitin sulfate or with synthetic carboxymethyl cellulose. In vitro studies revealed that particles with chondroitin sulfate, when compared to carboxymethyl cellulose, exhibited a superior macrophage-targeting capacity and a stronger anti-inflammatory capacity, along with a more pronounced in vivo therapeutic efficacy for UC after oral administration.

Another ligand for the CD44 receptor is the polysaccharide hyaluronic acid (Lima et al., 2021). This anionic, non-sulfated glycosaminoglycan commonly found in synovial fluids and in the extracellular matrix was exploited to coat nanoparticles and nanocrystals (X. Cai, Wang, He, et al., 2021; Feng et al., 2022; Luo et al., 2021; Lv et al., 2023; J. Xie et al., 2023; Y. Zhang, Ma, You, et al., 2023; X. Zhao, Su, et al., 2023), typically leading to an improved uptake from the inflammatory cells thanks to its active targeting. Other components can be added to hyaluronic acid-based systems, to impart different functionalities and improvements to the delivery systems besides the active targeting to colon inflamed cells. For instance, resistance to gastric degradation and premature drug release can be obtained by coating the nanoparticles with Eudragit® S100 (X. Cai, Wang, He, et al., 2021; Y. Zhang, Ma, You, et al., 2023). The inclusion of Pluronic® F127, a synthetic block copolymer, can endow the nanotherapeutic with enhanced mucus-penetration properties (D. Xie et al., 2022; J. Xie et al., 2023). It has been recently demonstrated that indigo/indirubin nanocrystals coated with hyaluronic acid and Pluronic F127 displayed a mucus penetration ability about 25-fold higher than the control group, and an enhanced cellular uptake twice than the uncoated nanocrystals (J. Xie et al., 2023). The improved therapeutic efficacy in dextran sodium sulfate (DSS)-treated mice with acute colitis was achieved thanks to the regulation of cytokines expression, of the immune responses via downregulating the expression of macrophages, neutrophils, and dendritic cells and maintaining intestinal flora homeostasis.

Lactoferrin (LF) is a glycoprotein of the transferrin family that can bind to LF receptors highly expressed in intestinal epithelial cells. It has been reported the production of LF nanoparticles with a dual targeting property, for example, by coating them with hyaluronic acid (Luo et al., 2021). The addition of a second coating layer of calcium pectinate provided gastro-resistant and colon-targeting features. One more example is the loading of nanoparticles into yeast cell wall microparticles, which target dectin-1 receptors in macrophages (Pu et al., 2021). This polymer also provides gastric protection as it is only degraded in the colon. Several other proteins have been used for producing nano-based oral delivery systems for UC, for instance, gelatine (Ahmad, Ansari, Mishra, et al., 2021), zein (X. Wang, Gu, et al., 2021), human serum albumin (Luo et al., 2020), and silk fibroin (Diez-Echave et al., 2021; Gou et al., 2019; S. Liu et al., 2022; Ma et al., 2022; D. Xie et al., 2022). Colon-targeting components such as, for example, Eudragit® S100 (Ahmad, Ansari, Mishra, et al., 2021), tannic acid (Luo et al., 2020), ferulic acid (C. Zhao, Yang, et al., 2023), and chitosan and/or alginate (Gou et al., 2019; S. Liu et al., 2022; Ma et al., 2022; X. Wang, Gu, et al., 2021) are often included in the formulation to prevent the drug from being prematurely released in the stomach and small intestine.

Even though such approaches promote the accumulation of nanoparticles in the colon, low cellular uptake and, consequently, low intracellular drug concentration, hinder its therapeutic efficiency. Nanoparticles' surface modification with ligands can facilitate their binding to specific inflamed cells in the colon site (Gou et al., 2019; S. Liu et al., 2022; Ma et al., 2022; X. Wang, Gu, et al., 2021). For instance, stimuli-responsive silk fibroin nanoparticles encapsulating curcumin and functionalized with chondroitin sulfate were described by Gou et al. Such system provided enhanced macrophage uptake and controlled curcumin release upon stimulation of intracellular pH, glutathione, and reactive oxygen species (ROS) (Gou et al., 2019). Most silk fibroin nanoparticles are obtained from the species *Bombyx mori*; silk fibroin nanoparticles from the species *Antheraea pernyi*, however, have shown intrinsic active targeting properties by specifically binding to integrin receptors, which are highly expressed on colonic epithelial cells and activated macrophages (Ma et al., 2022).

Overall, studies so far demonstrate that integrating biopolymers in oral nanotherapies for IBD is a flourishing research field. Chitosan is the most widely used due to its ability to provide mucosal attachment and consequently prolong the GI residence time, while alginate is often included in the formulation to protect against gastric degradation and prevent the premature release of the drug. The delivery of the drug in the colon and the enhanced cellular uptake is in some cases obtained thanks to active targeting strategies, such as the CD44 receptor in inflammatory cells given by, for instance, the biopolymers chondroitin sulfate and hyaluronic acid. From this picture, it is evident that different

components need to be included in the nanoformulation to provide a specific functionality and result in an effective nanomedicine for the treatment of IBD (Table 1).

2.1.2 | Lipid-based nanoparticles

Similarly to polymers, also lipids are well-established components for producing nanotherapeutics due to their biocompatible, biodegradable, and non-toxic properties. However, while lipids remain unrivaled excipients in nanomedicine for parenteral administration, they are more susceptible to degradation as their chemical structure presents functional groups that are prone to oxidation and hydrolysis (Sainaga Jyothi et al., 2022). Consequently, lipid-based nanoparticles are significantly less investigated than polymeric nanoparticles as drug delivery systems for the oral treatment of IBD. Among the numerous categories of lipid-based nanoparticles, liposomes stand out as the most explored systems for drug delivery purposes, including the treatment of IBD. Liposomes are typically composed of phospholipids arranged in a lipid bilayer surrounding an aqueous core. Such a resemblance to biomembranes not only provides excellent biocompatibility and safety profiles but also allows the incorporation and delivery of hydrophobic and hydrophilic actives. Both natural and synthetic phospholipids have been used to produce liposomes. Egg yolk and soybean are the two main sources of natural phospholipids. They are ideal materials for industrial pharmaceutical development processes thanks to their widespread availability and associated costs of goods, alongside considerations of sustainability and environmental impact during production (van Hoogevest & Wendel, 2014). Some examples are phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. Synthetic phospholipids are often obtained by modifications in the aliphatic chain, such as, for instance, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), and distearoylphosphatidylethanolamine (DSPE).

The GI mucus contains phospholipids, mainly phosphatidylcholine, which provide a hydrophobic surface and help to maintain an intact barrier function (Torres et al., 2013). Phosphatidylcholine was found to be substantially reduced in the mucus of UC patients, allowing the permeation of colonic bacteria, and promoting further inflammation (Karner et al., 2014). In a clinical trial, UC patients showed significant improvement in disease activity upon treatment with a modified-release phosphatidylcholine formulation (Karner et al., 2014). Phosphatidylcholine is the main phospholipid component in egg yolk and soybean lecithin (T. Wang et al., 1997; F. Zhao, Li, et al., 2023). It has been reported that lecithin and cholesterol liposomes present a slow degradation rate in simulated gastric fluid, leading to higher accumulation of active compounds, for instance curcumin (C. Wang, Han, et al., 2021) and superoxide dismutase (C. Zhang, Hu, Yuan, et al., 2023), in the intestine. Both of these compounds can reduce oxidative stress and inflammation. This gastro-resistance feature can be explained by the limited lipase activity in the stomach (5%–30%) and major lipid digestion in the intestine (Golding & Wooster, 2010; C. Wang, Han, et al., 2021). Strategies can be further employed to enhance the efficacy of the system, for instance, adding anti-inflammatory ingredients to compose the lipid bilayer (J. H. Kim et al., 2019). Krill oil is rich in Omega-3, which can attenuate colonic damage and inflammation. Together with phosphatidylcholine (DOPC and DSPC) and cholesterol, krill oil was applied to produce budesonide-loaded liposomes (J. H. Kim et al., 2019). Another example is the lipidation of the active ingredient to enhance the cell membrane permeability (Xian et al., 2023). Budesonide was linked to linoleic acid by an ester bond which could be hydrolyzed by esterase activity in the intestinal tract, and this prodrug was assembled into liposomes together with phosphatidylcholine, cholesterol and DSPE-PEG_{2k}. Additional approaches that have been explored to maximize drug concentration in the inflamed intestinal tissue include the incorporation of nanoparticles into a gastro-resistant matrix (Wu et al., 2023; H. Yan et al., 2023) and nanoparticles' surface modification (Cui et al., 2022; H. Zhao et al., 2022).

The use of probiotics in UC treatment has been proven to improve the function of the epithelial barrier and to regulate the inflammatory response. However, the low stomach pH and enzymatic activity reduce considerably their survival rates. In view of this, Zhao et al. used nanozymes as a therapeutic nano-coating for liposomes encapsulating probiotics. The nanozymes could not only protect the probiotics from degradation, but also promoted a synergistically enhanced therapeutic effect (H. Zhao et al., 2022).

The activation of phosphatidylserine receptors on inflammatory macrophages located in the inflamed intestinal tissue led scientists to investigate this phospholipid as a surface ligand on liposomes. Phosphatidylcholine and cholesterol liposomes functionalized with phosphatidylserine were designed by H. Yan et al., and cell uptake experiments confirmed that nanoparticle internalization by lipopolysaccharide-stimulated murine Raw264.7 macrophages was heavily dependent on this surface modification (H. Yan et al., 2023). One more macrophage targeting approach explored the overexpression of folate receptors. Specific binding to these receptors was achieved by producing PEGylated liposomes

TABLE 1 Summary of the main biopolymers reported for the preparation of bioinspired nanocarriers for inflammatory bowel treatment, divided by function (nanoparticles [NPs] matrix, coating, and nanocomposite matrix) and administration route (oral, parenteral, and rectal).

Biopolymer	Function	Administration route	References
Chitosan	NPs matrix	Oral	(Ahmed et al., 2022; X. Cai, Wang, He, et al., 2021; Feng et al., 2022; Khater et al., 2022; Mahami et al., 2023; Maleki et al., 2023; Mohanbhai et al., 2022; L. Wang, Fu, et al., 2023; Xiong et al., 2023; Y. Yan et al., 2020; Y. Zhang, Ma, You, et al., 2023)
		Parenteral	(Soni et al., 2021)
	Coating	Oral	(Bai et al., 2022; Chen et al., 2020; Jin et al., 2021; Lei et al., 2023; S. Li, Jin, et al., 2021; Ling et al., 2019; Lv et al., 2023; Oshi et al., 2020; Tahara et al., 2011; N. Wang, Shao, et al., 2022; X. Zhang et al., 2019; Zhang, Yuan, Wu, et al., 2023; Y. Zhang, Ma, You, et al., 2023; Y. Zhang, Wang, Wang, et al., 2023)
	Nanocomposite matrix	Oral	(Gou et al., 2019; X. Li, Yu, et al., 2021; S. Liu et al., 2022; Ma et al., 2022; Rosso et al., 2021; Wu et al., 2023; Xiong et al., 2023)
Hyaluronic acid	NPs matrix	Oral	(X. Zhao, Su, et al., 2023)
		Rectal	(Vafaei et al., 2022)
	Coating	Oral	(X. Cai, Wang, He, et al., 2021; Feng et al., 2022; X. Li, Fang, et al., 2022; Luo et al., 2021; Lv et al., 2023; J. Xie et al., 2023; Y. Zhang, Ma, You, et al., 2023)
Alginate	NPs matrix	Oral	(Dong et al., 2021; L. Wang, Fu, et al., 2023; X. Zhao, Su, et al., 2023)
	Coating	Oral	(Jin et al., 2021; S. Li, Jin, et al., 2021; Oshi et al., 2020; N. Wang, Shao, et al., 2022; Y. Yan et al., 2020; X. Zhang, Yuan, Wu, et al., 2023)
	Nanocomposite matrix	Oral	(Andretto et al., 2023; Lei et al., 2023; Ling et al., 2019; X. Wang, Gu, et al., 2021; H. Yan et al., 2023)
Pectin	NPs matrix	Oral	(Ahmed et al., 2022)
	Coating	Oral	(Luo et al., 2021)
	Nanocomposite matrix	Oral	(Wu et al., 2023)
Chondroitin sulfate	Coating	Oral	(Gou et al., 2019; X. Wang, Gu, et al., 2021; X. Zhang et al., 2019)
		Parenteral	(Gou et al., 2019)
Gelatine	NPs matrix	Oral	(Ahmad, Ansari, Mishra, et al., 2021; Bhavsar & Amiji, 2008; Kriegel & Amiji, 2011)
		Parenteral	(Ahmad, Ansari, Mishra, et al., 2021)
Silk fibroin	NPs matrix	Oral	(Diez-Echave et al., 2021; Gou et al., 2019; S. Liu et al., 2022; Ma et al., 2022; D. Xie et al., 2022)
		Parenteral	(Gou et al., 2019)
Silk sericin	NPs matrix	Oral	(S. Xu, Yang, et al., 2022)
Zein	NPs matrix	Oral	(X. Wang, Gu, et al., 2021)
Albumin	NPs matrix	Oral	(Luo et al., 2020)
Glycogen	NPs matrix	Parenteral	(Y. Xu, Zhu, et al., 2022)
Lignin	NPs matrix	Oral	(C. Zhao, Yang, et al., 2023)
Inulin	Coating	Oral	(Q. Sun et al., 2021; J. Xie et al., 2023)
Lactoferrin	NP matrix	Oral	(Luo et al., 2021; Pu et al., 2021)
	Coating	Parenteral	(Y. Zhao et al., 2020)
Cellulose	Coating	Oral	(Y. Zhang, Wang, Wang, et al., 2023)
PLGA	NPs matrix	Oral	(Y. Huang et al., 2018)
		Rectal	(Le et al., 2021)
	Nanospheres	Oral	(Tahara et al., 2011)

with folate-functionalized cholesterol (Wu et al., 2023). The interaction between these liposomes and the intestinal mucus, however, has not been investigated. Strategies such as adjusting the size and shape of nanoparticles, as well as incorporating surface ligands like PEG, have been utilized to enhance their diffusion through the mucus (Zierden et al., 2021). We emphasize the importance of evaluating the mucoadhesion and penetration into the mucus, as nanoparticles might be retained in healthy tissues prior to reaching the inflamed sites.

Lipids extracted from other natural sources, for example ginger, have also been utilized in the development of liposomes for IBD therapies (Long et al., 2023; Yang et al., 2020). A specific group of ginger-derived nanoparticles, composed mostly of phosphatidic acid, digalactosyldiacylglycerol and monogalactosyldiacyglycerol, was effective in treating UC in vivo (M. Zhang et al., 2016). The lipids from these nanoparticles were extracted and used to produce liposomes encapsulating 6-shogaol (ginger potent active component) and its metabolites (Long et al., 2023; Yang et al., 2020).

Even though less explored than liposomes, lipid nanoparticles (Chen et al., 2020) and solid lipid nanoparticles (El-Dakroury et al., 2024; Sharma et al., 2019; Y. Zhang, Wang, Wang, et al., 2023) have also been reported as oral nanotherapeutics for IBD. Chitosan-coated esterase-responsive lipid nanoparticles were designed for the colon-targeted delivery of dexamethasone (Chen et al., 2020). Chitosan was also employed as coating material on fexofenadine-loaded solid lipid nanoparticles (El-Dakroury et al., 2024). A layer-by-layer technique, which alternates layers of sodium cellulose sulfate and chitosan, was applied to solid lipid nanoparticles composed of fatty acids (Y. Zhang, Wang, Wang, et al., 2023). In this case, drug delivery is triggered by the action of cellulolytic bacteria in the colon. Solid lipid nanoparticles composed of a binary mixture of fatty acids and triglycerides were reported to improve curcumin loading capacity by 1.23-fold compared to fatty acid alone (Sharma et al., 2019). Our research group recently developed gastroresistant 3D-printed tablets composed of phospholipid-based lipid mesophases (Carone et al., 2024). The tablets were loaded with obeticholic acid, a semi-synthetic agonist of farnesoid-X-receptor that has shown anti-inflammatory and anti-fibrotic activity in a chronic model of colitis (Biagioli et al., 2021). We showed that, through a self-emulsification process, nanosized lipid colloidal structures contributed to enhancing drug solubility and cellular uptake.

Overall, these studies demonstrate that liposomes are considerably further explored than other lipid-based nanoparticles for the oral treatment of IBD. Slow liposomal degradation in stomach conditions was reported in some studies, which provides enhanced drug concentration in the inflamed intestine. Gastro-resistant strategies applying biopolymers, either as surface coating or matrices for the incorporation of nanoparticles, have been utilized to enhance the system's efficiency. Interestingly, the phospholipid liposomal composition could be tuned considering physiopathological conditions of the disease, such as reduced phosphatidylcholine in the mucus and activation of phosphatidylserine receptors in macrophages (Table 2).

2.1.3 | Nanocomposites

As mentioned in the previous sections, nano-based drug delivery systems offer numerous advantages for the oral treatment of IBD. However, the nanocarrier's susceptibility to enzymatic activity or gastric pH might result in premature drug release, leading to a diminished therapeutic effect, depending on its composition. In UC and most cases of CD, the inflammation is restricted to the terminal ileum and/or colon, hence it is favorable that the nanocarrier retains stability until it reaches this specific site to ensure optimal efficacy. Two strategies can be applied to ensure targeted delivery: (i) nanoparticles' surface functionalization with excipients that promote colonic or ileocolonic delivery, and (ii) nanoparticles' incorporation into macro- or micropolymeric matrices. The latter approach creates systems known as nanocomposites (Andretto et al., 2021). Besides assisting in site-specific drug delivery, nanocomposites can also improve the system's mechanical strength, enhance drug stability, and modulate the drug release kinetics. Hydrogels represent the most well-known and explored category of nanocomposite macrosystems. The use of alginate hydrogels, either as a single component (Lei et al., 2023) or in combination with chitosan (Gou et al., 2019; S. Liu et al., 2022; Ma et al., 2022; D. Xie et al., 2022; Xiong et al., 2023; X. Zhang et al., 2019) is a simple yet highly efficient strategy for colon-targeted drug delivery. A peptide-based hydrogel that self-assembles in physiological conditions has been recently reported (Andretto et al., 2024). Hydrogels can be used as building blocks for the preparation of solid nanocomposite macrosystems, for example, sponges. These solid systems present a dry and porous matrix which provides high storage stability and improved mucoadhesion, respectively. Chitosan sponges incorporating a nanoemulsion with mucopenetrating properties showed enhanced intestinal residence time in vivo (Rosso et al., 2021).

TABLE 2 Summary of the main lipids reported for the preparation of bioinspired nanocarriers for IBD treatment, divided by function (liposomal bilayer, lipid nanoparticles [LNPs] and solid lipid nanoparticles [SLNs] matrix, and lipid mesophase [LMP]) and administration route (oral, parenteral, rectal, intraperitoneal, and transdermal).

Lipid	Function	Administration route	References
Phosphatidylcholine (PC)	Liposomal bilayer	Oral	(Xian et al., 2023; H. Yan et al., 2023)
		Parenteral	(Y. Z. Zhao et al., 2019)
		Intraperitoneal	(Q. Tang et al., 2020)
Phosphatidylserine (PS)	Liposomal bilayer	Oral	(H. Yan et al., 2023)
Dioleoylphosphatidylcholine (DOPC)	Liposomal bilayer	Oral	(J. H. Kim et al., 2019)
		Rectal	(Lee et al., 2022)
Distearoylphosphatidylcholine (DSPC)	Liposomal bilayer	Oral	(J. H. Kim et al., 2019)
		Parenteral	(Oh et al., 2023)
Dioleoylphosphatidylethanolamine (DOPE)	Liposomal bilayer	Transdermal	(Y. Zhang et al., 2020)
		Rectal	(Lee et al., 2022)
	LNPs matrix	Oral	(Wei et al., 2023)
Dioleoylphosphatidylserine (DOPS)	Liposomal bilayer	Rectal	(Lee et al., 2022)
Cholesterol	Liposomal bilayer	Oral	(Cui et al., 2022; J. H. Kim et al., 2019; C. Wang, Han, et al., 2021; Wu et al., 2023; Xian et al., 2023; H. Yan et al., 2023; C. Zhang, Hu, Yuan, et al., 2023)
		Parenteral	(Oh et al., 2023; Y. Zhao et al., 2020; Y. Z. Zhao et al., 2019)
		Intraperitoneal	(J. Huang et al., 2023; Q. Tang et al., 2020)
		Transdermal	(Y. Zhang et al., 2020)
		Rectal	(Lee et al., 2022)
Egg/soybean lecithin	Liposomal bilayer	Oral	(Cui et al., 2022; Sharma et al., 2019; C. Wang, Han, et al., 2021; Wu et al., 2023; C. Zhang, Hu, Yuan, et al., 2023)
		Parenteral	(Y. Zhao et al., 2020)
PEGylated Distearoylphosphatidylethanolamine (DSPE-PEG)	Liposomal bilayer	Oral	(Wu et al., 2023; Xian et al., 2023; H. Zhao et al., 2022)
		Parenteral	(Oh et al., 2023; Y. Zhao et al., 2020; Y. Z. Zhao et al., 2019)
		Intraperitoneal	(Q. Tang et al., 2020)
		Transdermal	(Y. Zhang et al., 2020)
	NPs matrix	Rectal	(Le et al., 2021)
Dioleoyl-3-trimethylammonium-propane (DOTAP)	Liposomal bilayer	Intraperitoneal	(J. Huang et al., 2023)
	NPs matrix	Rectal	(Le et al., 2021)
Ginger natural lipids	Liposomal bilayer	Oral	(Long et al., 2023; Yang et al., 2020)
Stearic acid	SLN matrix	Oral	(Sharma et al., 2019)
Glyceryl tristearate	SLN matrix	Oral	(Sharma et al., 2019)
Glyceryl dibehenate	SLN matrix	Oral	(Y. Zhang, Wang, Wang, et al., 2023)
Monolinolein	LMP	Rectal	(Carone et al., 2023)

Nanocomposite microsystems such as microspheres, microgels, and microcapsules have a size below 1000 μm. Compared to conventional macrosystems, their smaller size allows for better coverage of the wide intestinal surface area, thanks to their higher surface area to volume ratio and the possibility of efficiently accommodating on the intestinal epithelium (Andretto et al., 2021). At the same time, the larger size of nanocomposite microsystems compared to the nanoparticles alone avoids premature uptake in the small intestine (Zhu et al., 2012). Because of its colon-targeting and bioadhesive properties, alginate has also been used to produce nanocomposite microsystems, such as microspheres (X. Wang, Gu, et al., 2021), microbeads (Andretto et al., 2023), and microparticles (Ling et al., 2019; H. Yan et al., 2023). Additional polymers have been included in these systems to improve their physicochemical properties. For instance, chitosan coating on alginate microgels can reduce drug leakage (Ling et al., 2019) and xanthan gum can prevent the rapid diffusion of nanoparticles during the formation of alginate shells on microspheres (X. Wang, Gu, et al., 2021).

We have seen that, in addition to the production of nanoparticles, biopolymers have been used to design nanocomposites. These systems can be presented as solid dosage forms, such as tablets, capsules, and sponges, making them advantageous for oral delivery. However, the studies reviewed herein primarily evaluated semi-solid nanocomposites in vivo, possibly due to limitations in assessing solid dosage forms in small animal models. Therefore, formulation optimization might be required for the clinical—and possible commercial—application of these nanocomposites in treating IBD.

2.2 | Parenteral administration

Management of IBD via the parenteral route is recommended for patients who do not respond to oral therapies (Cushing & Higgins, 2021; Gajendran et al., 2019; Langan et al., 2007). The most common parenteral administration route is the intravenous (i.v.), which provides a rapid onset of action and complete bioavailability (Orlando de Jesus, 2023). This route also offers an alternative for drugs that are unstable and/or poorly absorbed in the GI tract. However, the enhanced systemic drug exposure enabled by i.v. infusions can lead to intensified side effects compared to oral therapies, as with oral administration the drug preferentially accumulates in the intestine, diminishing the side effects due to systemic exposure from the circulating system. Nanoparticles offer a strategy to enhance drug concentration in the inflamed tissue after i.v. infusions via EPR effect.

Polymeric (Ahmad, Ansari, Kumar, et al., 2021; Gou et al., 2019; Soni et al., 2021; Y. Xu, Zhu, et al., 2022) and lipid-based (Oh et al., 2023; Y. Zhao et al., 2020) nanoparticles have been investigated as carriers for the i.v. administration of natural compounds, for example, melatonin, curcumin, ginsenoside Rh2, and patchouli alcohol. Such compounds show promising therapeutic potential for treating IBD due to their potent anti-inflammatory activity and reduced side effects compared to conventional treatments. Encapsulating natural products into nanoparticles can overcome their limitations of poor bioavailability and short half-life, thus expanding their clinical application.

Soni et al. reported an enhanced anti-inflammatory effect of melatonin-loaded chitosan nanoparticles compared to bare melatonin. Additionally, the passive targeting effect enabled by nanoparticles was demonstrated by the higher drug retention in the intestine (mainly in the colon) compared to other organs (Soni et al., 2021). Stimuli-responsive nanoparticles can prolong the drug circulation time and promote rapid drug release when exposed to specific triggers (Y. Xu, Zhu, et al., 2022). The unique acidic and redox environment of the inflamed tissue was employed as a trigger for the localized drug release from urocanic acid and α-lipoic acid-modified glycogen nanoparticles (Y. Xu, Zhu, et al., 2022). Gou et al. combined active targeting and stimuli-responsiveness approaches into silk fibroin nanoparticles. Surface functionalization with chondroitin sulfate provided specific targeting capability toward activated macrophages and, once the particles were internalized, the low pH and high glutathione (GSH) and ROS levels triggered drug release (Gou et al., 2019).

LF was investigated as a liposomal ligand to target the delivery of patchouli alcohol specifically to inflammatory macrophages located at the inflamed intestinal tissues (Y. Zhao et al., 2020). Patchouli alcohol, a tricyclic sesquiterpenoid, has been reportedly able to suppress the nuclear factor-kappa B (NF-κB)-mediated intestinal inflammation in animal models. The inflammation regression promoted by this liposomal formulation is associated with the suppression of mitogen-activated protein kinase (MAPK) and NF-κB, which are essential inflammatory signaling pathways. Liposomes targeting the spleen have also been explored for immunomodulation, as this organ regulates local and systemic immune responses. Oh et al. screened various PEGylation strategies and obtained efficient spleen-targeted liposomes loading hydrogen sulfide, which is a gasotransmitter that carries out anti-inflammatory functions. This formulation showed a higher systemic immune modulative effect compared to conventional long-circulating liposomes

(Oh et al., 2023). Intraperitoneal (Q. Tang et al., 2020) and transdermal (Y. Zhang et al., 2020) administrations routes have also been investigated for the systemic delivery of natural compounds via liposomal formulations.

Parenteral therapies are frequently used in the management of IBD, especially in moderate-to-severe disease. This administration route offers an effective alternative for drugs that are poorly water-soluble and/or have poor membrane permeability, as well as for drugs that are unstable in the GI tract. We have observed, however, that current research on nanotherapies with small molecules focuses on oral therapies rather than parenteral ones. Such a scenario could be explained by the advances in the development of oral delivery systems with colon targeting and enhanced cellular drug uptake properties and a reduced patient's acceptance of invasive administration routes to treat a chronic condition that ultimately cannot be cured.

2.3 | Rectal administration

The first line treatment for mild-to-moderate UC proctitis are rectal formulations—mainly suppositories containing 5-ASA—since, at this stage of the disease, inflammation is limited to the rectum. The mechanism of action of 5-ASA is partially elucidated. It appears to act locally on the colorectal mucosa, reducing inflammation through various mechanisms (Desreumaux & Ghosh, 2006). One important finding is the activation of the peroxisome proliferator-activated receptor (PPAR)-gamma, which is highly expressed in the colon and plays a role in regulating intestinal inflammation (Iacucci et al., 2010). Rectal formulations provide localized drug delivery directly to the affected area, thereby reducing systemic side effects. Rectal administration also provides an alternative for drugs susceptible to degradation in the GI tract. However, this administration route is less accepted by patients compared to oral administration, potentially decreasing patient compliance. Additionally, rectal formulations can only reach a certain extent of the colon. In cases of left-sided or extensive colitis, where inflammation extends deeper into the colon, a combination of enemas and oral therapies is recommended. Enemas often present short residence time and low delivery efficiency, though. Such limitations can be circumvented by nano-based drug delivery systems.

The application of biopolymers for the development of nano-based therapies for rectal administration has been limited compared to oral and parenteral administration routes. Hyaluronic acid nanoparticles have been designed for the encapsulation of budesonide (Vafaei et al., 2022). However, rectally applied liquid formulations are susceptible to leakage, and the mucoadhesion property of this formulation was not investigated by Vafaei et al. Lipid-polymer nanoparticles with PEG coating and folate surface functionalization have been proposed by Le et al., and prolonged mucosal residence time, high mucus permeability and enhanced cellular drug uptake were observed. The authors incorporated the enzyme superoxide dismutase into these particles and investigated their therapeutic potential for the local treatment of IBD through rectal administration, aiming to avoid the hydrolysis and degradation of the enzyme in the GI tract (Le et al., 2021).

Negatively charged small unilamellar vesicles (SUV) were investigated for rectal delivery of fibronectin, a protein that plays an essential role in wound healing process (Lee et al., 2022). In the context of IBD, the level of fibronectin in the plasma is significantly decreased. It has been reported that supplying cells with unfolded fibronectin improved its efficiency. Interestingly, the developed SUVs not only provided enhanced cell attachment but also induced the unfolding of fibronectin.

Carone et al. explored the unique rheological properties of lipid mesophases for the rectal delivery of tofacitinib and tacrolimus. The formulation, based on the lipid monolinolein, presents a low viscosity lamellar phase at room temperature, which provides an easy application by the patient, and a high viscosity cubic phase at the rectal temperature, providing high drug retention (Carone et al., 2023).

The development of rectal nano-based formulations for IBD is considerably lacking. This might be attributed to their current application being limited to proctitis and left-sided colitis. However, the limited systemic exposure and consequent reduction in adverse effects offered by such formulations are beneficial aspects for patients. Therefore, there is a need for the development of effective rectal formulations with prolonged drug retention in the colon.

3 | NANOCARRIERS FOR BIOTHERAPEUTICS AND CELL-BASED TREATMENTS

Harnessing the efficacy of biotherapeutics (i.e., drug therapy products where the active substance is extracted or produced from a biological source) (Johnson, 2018) with nanomedicine offers an innovative approach to advancing

medical treatments for IBD (Y. Shi & Lammers, 2019; L. Tang et al., 2021). First, encapsulating biotherapeutics such as antibodies, cytokines, or nucleic acids within nanocarriers can protect them from degradation and improve their stability. Second, as seen in Section 2, a controlled release system can provide a sustained and localized release of actives, ensuring prolonged effects. Lastly, taking advantage of the large surface area and countless possibilities for surface modification, the delivery systems can be engineered to interact with the mucosal lining of the GI tract, potentially modulating the permeability of the barrier and reducing inflammation. Indeed, nanomaterials themselves can be designed to directly interact with immune cells (vide supra) augmenting the inflammatory efficacy of biologics. An overview of the nano-based formulations for biotherapeutics and cell-based treatments covered in this section is presented in Figure 1c.

The use of nanocarriers has the potential to ensure a neglectable degradation of the payload by gastric and intestinal enzymes and, in turn, maximizes their residence time into the target inflamed site. Other enzymes, such as DNases, can degrade anti-sense oligonucleotides, an emerging class of treatments already involved in clinical study (Monteleone et al., 2015). With the aid of nanocarriers, high stability and efficacy of the incorporated nuclear factor-kappa B (NF-κB) anti-sense oligonucleotides could be effectively achieved, as demonstrated by the delivery of the oligonucleotides in a rodent colitis model (Collnot et al., 2012; Tahara et al., 2011). As discussed in Section 2.1.2, lipids extracted from ginger can be utilized to produce lipid-based nanocarriers. M. Zhang et al. complexed such lipids with siRNA against CD98 (siRNA-CD98). This system decreased the expression of CD98, a mediator that plays an important role in colitis and colitis-associated cancer (M. Zhang et al., 2017).

Enzymatic degradation of plasmids (IL-10-expressing plasmid DNA) and nucleic acids (TNF-α specific siRNA) after oral administration have been suppressed employing a nanocomposite system composed of type B gelatin nanoparticles further entrapped in poly(epsilon-caprolactone) microspheres, forming a nanoparticles-in-microsphere oral system. Gene silencing and high anti-inflammatory cytokine expression both led to an increase in body weight and reduced tissue inflammation in an acute colitis model (Bhavsar & Amiji, 2008; Kriegel & Amiji, 2011). An alternative carrier system for TNF-α siRNA based on mannose-modified trimethyl chitosan-cysteine nanoparticles was developed by He et al. Interestingly, the modulation of the polymer crosslinking process allows for a similar siRNA protection in physiological conditions, while macrophage uptake showed various siRNA release profiles (He et al., 2020). Apart from preventing degradation, nanoparticles (formulated from a polymer, poly-(1,4-phenyleneacetone dimethylene thioketal)) can also enhance the TNF-α siRNA delivery after oral administration solving its poor cell membrane permeability, thus suppressing colonic TNF-α protein expression in an in vivo model of colitis. Moreover, to abolish the side effects caused by the systemic depletion of cytokines, this system degrades selectively in response to ROS at sites of intestinal inflammation, diminishing TNF-α messenger RNA levels in the colon and protecting mice from UC (Wilson et al., 2010).

A combination of controlled release and active targeting is achieved by using poly(lactic-co-glycolic acid) loaded with TNF-α siRNA and decorated with galactosylated chitosan. These modified particles alleviated the inflammation more efficiently than unmodified ones. Indeed, the galactosylated chitosan interacts with the mucosal barrier and enhances the residence time of the system into the colon and in turn the drug absorption (Y. Huang et al., 2018).

Liposomes are also often used as carriers to efficiently deliver siRNA. A promising example employs cationic vesicles, composed of DOTAP and cholesterol, which host and release a siRNA silencing a pyrin domain containing protein 3 (NLRP3) inflammasome, recognized as an important contributor to macrophage activation and immune response (J. Huang et al., 2023). Still within the domain of lipid-based delivery systems, lipid nanoparticles (LNPs) also serve as a useful tool for the oral delivery of siRNA therapeutics to colon epithelial cells, macrophages, and dendritic cells. Indeed, the delivery of TNF-α siRNA mitigates gut inflammation in a DSS-induced murine inflammation model by inhibiting the infiltration and differentiation of CD4+ T cells into Th17 and T_{reg} cells (Verma et al., 2022).

Moreover, pandemic and LNP-based COVID vaccines paved the way for delivering through these particles not only siRNA but also (and mainly) messenger RNA (mRNA) into cells, instructing them to produce an immunogenic but harmless spike protein. Thus, the same strategy can also be employed in IBD, where epithelial mRNAs loaded-LNPs regulate intestinal stem cell proliferation and facilitate intestinal regeneration in mice and colonic tissues derived from patients with UC (Wei et al., 2023).

Although the above-mentioned promising strategies employ siRNA, plasmid DNA and mRNA-loaded nanomedicine, nowadays the majority of patients with severe UC achieve immunosuppression through antibody anti-(TNF-α) such as IFX (Catalan-Serra & Brenna, 2018; Park & Jeen, 2015; Wehkamp & Stange, 2018). Multiple infusion-mediated administrations are required, resulting in important limitations, including systemic toxicity and loss of sustained response to therapy with time-producing symptom flares (Ben-Horin et al., 2015). Exploring alternative delivery avenues could allow the drugs to be released slowly directly at the inflammation site with minimal exposure to distant tissues reducing either the dose or its administration frequency. Remarkably, the intestinal epithelial barrier of

the inflamed intestine is damaged, favoring antibody entry into the mucosal layer, where these play a therapeutic role, with no need for systemic exposure (Moroz et al., 2016). Thus, nano-in-microparticles based on chitosan/carboxymethyl chitosan and alginate were successfully developed for oral administration of IFX in colitis (X. Li, Yu, et al., 2021). However, this system is restricted by poor antibody loading and complex preparation methods. A promising approach is to use the IFX as stable nano-core cross-linked with the ROS-responsive moieties. When using this carrier-free antibody backpack, with an extremely high drug loading, the monoclonal antibody release is triggered by ROS. After oral administration, the nanocomplex showed extended retention time and caused increased antibodies accumulation in the inflamed intestinal tissues (X. Li, Fang, et al., 2022). A ternary nanocomposite based on liposomes, aminoclay and Eudragit® S100 was also reported for the delivery of IFX, exhibiting after oral administration a significant anti-inflammatory effect and a remarkably decreased TNF-α level in a DSS-induced mouse colitis model (J. M. Kim et al., 2020).

Besides antibodies, recombinant proteins, such as human LF have also been delivered by using silk sericin nanospheres (SS-NS-rhLF) with a spherical morphology with an average diameter of 123 nm. The negatively charged sericin achieves efficient adhesion to the inflamed colon of mice and a good therapeutic effect inhibiting the activation of the NF-κB inflammatory pathway in mice (S. Xu, Yang, et al., 2022). Other endogenous proteins secreted by inflamed epithelial cells such as Annexin A1 (AnxA1) are combined with lipid nanocapsules: intraperitoneal administration of nanocapsules loaded-protein in DSS-induced colitis mice reduced animal weight loss, diarrhea, and disease activity index. More interestingly, the treatment induces the skewing of macrophages into M2 phenotype in the lamina propria inducing resolution of inflammation and tissue repair (Broering et al., 2022). Using a combination of poly(aspartic acid) and sodium poly(aspartate) derived polymers, protein inhibitor of activated STAT1 (PIAS1; a SUMO 3 ligase which control NF-κB-mediated inflammation) was also successfully delivered, resulting in dampened gut inflammation in a murine colitis model after oral administration (Yavvari et al., 2019). A step further has been taken by Y. Z. Zhao et al., who combined keratinocyte growth factor (KGF) protection and active targeting. Liposomes improved KGF stability while neutrophil membrane vesicle (NEM; used to decorate the particles' surface) allowed to achieve a specific internalization by the inflammatory cells and thus ameliorate the colitis in DSS-induced mice after intravenous injection (Y. Z. Zhao et al., 2019). Macrophage membrane-decoration nanomedicine was also used by T. Sun et al., who developed a ROS-sensitive rosiglitazone-loaded β-cyclodextrin core coated by macrophage-membrane. The nanosystem exhibited excellent targeting ability to the inflammatory colon and a macrophage-polarizing effect (from pro-inflammatory M1 to anti-inflammatory M2), which resulted in remarkable anti-inflammatory performance in colon tissue (T. Sun et al., 2020).

In addition to the above therapeutic approaches, stem cells, including hematopoietic stem cells (HSC), mesenchymal stem cells (MSC), and intestinal epithelial stem cells (ISC), have received more attention as an effective therapeutic tool with intrinsic repair ability toward IBD treatment boosted with nanomaterial loads (Rogler, 2015). These can improve intestinal lesions by immunomodulation and tissue repair after homing to the inflamed intestine.

Although all the above-mentioned therapeutic modalities are effective in ameliorating IBD at least in preclinical studies, the practical therapeutic outcome relying on the single mechanism is still unsatisfactory. In this context, synergistic treatment via multiple therapeutic mechanisms for IBD treatment needs to be employed (Y. Zhang, Wang, Sun, et al., 2023). To achieve stable encapsulation and simultaneous delivery of siRNA and hydrophilic drugs for the treatment of IBD, a macrophage-targeting, reversibly crosslinked polymersomes was developed. The composite system could efficiently encapsulate TNF-α siRNA and corticosteroid drug dexamethasone sodium phosphate in the inner hydrophilic core, inducing efficient gene silencing, but also mediate potent and cooperative anti-inflammatory effects in inflamed colons of IBD (X. Xu et al., 2019). Similarly, a ROS-responsive nanoparticle for multi-mechanism synergistic therapy has been conceived. The system protects the anti-inflammatory peptide Ac2-26 from degradation in the GI tract and releases it in response to highly expressed ROS at diseased sites, inhibiting the expression of multiple proinflammatory mediators; regulates the inflammatory microenvironment; attenuates infiltration of inflammatory cells; increases phenotypic switching of macrophages; reshapes the composition of the gut microbiota (C. Li et al., 2019). More recently, a nanomaterial that targets multiple proinflammatory factors in IBD was developed by employing a drug-free, biodegradable nanomedicine that scavenges proinflammatory cell-free DNA (cfDNA) and ROS. The nanosystem was built by conjugating polyethylenimine (PEI) to antioxidative diselenide-bridged mesoporous organosilica nanoparticles (MONs) to achieve the decorated nanoparticles (MON-PEI). These orally administered MON-PEI exhibited high cfDNA binding affinity and ROS-responsive degradation attenuating colonic and peritoneal inflammation in mouse colitis models (C. Shi et al., 2022).

Even though the combination of nanomedicine and biotherapeutics has gained increasing attention and nanomedicine sciences are focusing on expanding the portfolio of systems to various sizes, materials, and surface interactions, general concerns have been brought up on the level of nanocarriers' safety and interaction with human GI tract and immune cells. Therefore, in the near future, nanomedicine needs to be designed to interact with major immune regulators such as macrophages and reprogram them toward an anti-inflammatory phenotype.

4 | BIODERIVED NANOMEDICINE FOR IBD TREATMENT

Extracellular vesicles (EVs) are membrane-defined particles, of heterogenous size and composition, shed by cells in pathological and physiological conditions (Welsh et al., 2024). Besides the luminal cargo composed of nucleic acid and soluble proteins and a multifaceted membrane, with its own signature of mesoscale properties and lipid/protein/glycan composition, proteins can be either embedded in or associated with the membrane as biomolecular corona (Radeghieri & Bergese, 2023). Although it is widely acknowledged that EVs could be an ideal system for therapeutic applications thanks to their extraordinary tropism and innate ability to deliver biomacromolecules, crucial regulatory aspects on the use of EVs in humans are still far from being standardized (Beetler et al., 2023). At present, achieving comprehensive characterization and absolute purity of biogenic EV products poses challenges. Even in the hypothetical scenario of successful isolation of highly homogeneously distributed EVs, variations in content, morphology, and membrane composition, factors that significantly influence the functional and therapeutic efficacy of the product, might still be present in the pooled biogenic sample (Herrmann et al., 2021). We showcase below some studies employing EVs as nanocarriers for IBD treatment, still at a preclinical level. For a comprehensive review of the translational challenges of biogenic medicine, we refer the reader to Beetler et al. (2023).

4.1 | Oral delivery of EVs

Oral delivery of biotherapeutics and cell-derived material presents challenges, such as protection of the cargo in the harsh conditions of the GI tract. A way to overcome this hurdle is to work with composite systems able to withstand proteolysis and enzymatic degradation, enabling a controlled and targeted release only in correspondence with the affected tissue. It has been recently shown that, by embedding EVs harvested and purified from cells overexpressing interleukin 10 (IL-10) as immunomodulatory therapeutic cargo in a mucoadhesive scaffold of chitosan and alginate, IL-10-loaded EVs could be protected by degradation in the GI tract as proved by in vivo studies in mice with DSS-induced colitis (J. Liu et al., 2023). To target efficiently the GI mucosa, Liu and colleagues decorated the surface of EVs with PEGylated lipids derivatized with galactose to enhance the accumulation of IL10-EVs in inflammatory macrophages infiltrating the colonic lamina propria. The use of a 3/7 weight ratio of chitosan and alginate gel as delivery enabled the specific release of the EV cargo in the colon, as suggested by in vitro data and confirmed in bioavailability studies in mice.

By choosing a different source of EVs, the intrinsic resistance to digestion of the vesicles can be remarkably increased. EVs from bovine milk (B-mEVs) and human milk (H-mEVs), for instance, have been shown to survive the hostile environment in the GI tract and to be transported to the basolateral side of the intestinal barrier (Tong et al., 2023). Besides their intrinsic ability to restore gut barrier integrity at multiple levels and to ameliorate inflammation in experimental IBD models (Reif et al., 2020; Tong et al., 2021), B-mEVs have been also recently tested for their ability to translocate into differentiated Caco-2 monolayers and 3D intestinal organoids from mucosal biopsies from a patient with mild chronic gastritis, to carry a model siRNA molecule, loaded with electroporation (encapsulation efficiency 5%), and transfect a macrophage cell line, and to deliver anti-TNFα siRNA in vivo following gavage and ameliorate TNBS-induced UC in rats (Y. Zhang, Belaid, Luo, et al., 2023). Zhang and colleagues envisaged the delivery of mEVs into enteric-coated capsules to ensure that membrane-associated proteins would be protected from stomach enzymes.

Interestingly, likely due to the complexity of milk as EV-containing matrix, different fractions of EVs obtained with different ultracentrifugation protocols could have substantial biological effect in vivo, specifically a pellet at centrifugation speeds above 100,000 *g* (P100K EVs) and a pellet obtained at lower speed (35′000, P35K EVs). As shown by Benmoussa and colleagues, B-mEVs can modulate cytokine production in the colon of healthy and DSS-treated mice differently (P35K EVs exerting more immunomodulating properties than P100K EVs) while P100K EVs can down-regulate colitis-associated microRNAs enhancing the level of the anti-inflammatory effector A20 and restoring expression levels of COX2 and ZO-1, two genes involved in inflammation and cell junction, respectively. While a more

comprehensive investigation of the native therapeutic cargo of EVs has been conducted by various research groups, as recently reported (Mignini et al., 2024; Shen et al., 2022), EVs are not widely and intensively used as nanocarriers in IBD. A modification of the EV carriers' surface can improve their targeting capacity and their colon-specific nature, as demonstrated by Deng and colleagues derivatizing the surface of EVs from mesenchymal stem cells (MSC) with a layer-by-layer (LbL) coating (Deng et al., 2023). Layering N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride (HTCC) and oxidized konjac glucomannan (OKGM) polysaccharides, LbL MSC-EVs administered via gavage to DSS-treated mice attenuated colitis repair the intestinal barrier by regulating oxidative stress and apoptosis and inhibiting the expression of proinflammatory cytokines and mieloperoxidase activity.

Despite the great promise held by MSC-derived systems, the low yield, and the complicated regulatory landscape for biotherapeutics of human origin are bottlenecks entangling clinical translations. For this reason, the most promising studies on oral delivery of EVs to date appear to be the ones considering food-derived EVs (plants [J. Li et al., 2024] and milk above all), particularly resistant at lower pH values and enzymatic degradation.

Studies have shown that turmeric-derived EVs, for instance, are able to reach the colon of rodents following oral administration and to exert anti-inflammatory activity, inhibit macrophage infiltration in the lumen and modulate the composition of the gut microbiota, specifically increasing the relative abundance of *akkermansia*, *lactobacillus*, *clostridia_UCG-014*, and *Bifidobacterium* (Gao et al., 2022).

EVs are secreted by all biological cell types, including bacteria. After having identified that IBD patients are characterized by low proportions of some bacteria such as *F. prausnitzii* with respect to healthy individuals, it has been shown that orally administered *F. prausnitzii* EVs (fp-EVs) would contribute to the amelioration of DSS-induced colitis in mice by modulating intestinal mucosal barrier function and the immunological profile (Ye et al., 2023). More in general, analysis of gut microbe-derived EVs has greater potential than analysis of the stool microbiome as a tool for investigating the pathogenesis of IBD (Heo et al., 2023).

4.2 | Intravenous delivery of EVs

Most studies concerning intravenous delivery of EVs deal with intrinsically bioactive vesicles from mesenchymal stem cells or intestinal cells, with little or no modification of the therapeutic cargo. For this reason, we did not cover these studies in this review, and we refer the readers to recent comprehensive systematic reviews on the topic (Kahmini & Shahgaldi, 2021; Ocansey et al., 2020).

One example worth mentioning here is based on the development of macrophage-derived coated cubic Pd (Pd@M), a biomimetic nanomedicine, synthesized as an efficient ROS scavenger for the treatment of UC and administered intravenously to mice with DSS-induced colitis (Cheng et al., 2023). The authors reported remarkable healing properties. The ROS-scavenging properties of Pd, synergistically combined with targeting properties of macrophage-derived EVs resulted in a composite bio-organometallic system specifically binding to intercellular cell adhesion molecule-1 (ICAM-1) and P-selectin, highly expressed on UC inflammation-impaired endothelium.

4.3 | Rectal delivery of EVs

A recent study successfully developed a microfluidics-based platform to produce bioadhesive microcarriers encapsulating EVs from mesenchymal stem cells engineered to overexpress IL-27, demonstrating their potential for targeted delivery, anti-inflammatory efficacy, and barrier repair in the treatment of IBD (Nie et al., 2023). By carefully optimizing the encapsulation process, using gentle handling techniques, maintaining physiological conditions, selecting biocompatible materials, and conducting thorough characterization, EVs can be included in gelatin methacrylate via microfluidics without interfering with their biological properties. This approach ensures that the therapeutic potential of EVs is preserved for effective targeted delivery in biomedical applications if endowed with a suitable carrier to ensure ideal mucoadhesivity and intestinal retention.

5 | CONCLUSION AND FUTURE PERSPECTIVES

Bioinspired and bioderived materials have shown great potential in the treatment of IBD, serving not only as drug delivery vehicles but also for their therapeutic effects. The bioavailability and biocompatibility of nano-based formulations

can be enhanced by the utilization of biomaterials. Moreover, surface functionalization of nanoparticles with colon-targeted components has been extensively explored, enhancing treatment efficacy while minimizing systemic drug absorption and toxicity to healthy tissues. We have observed a major development of colon-targeted nano-based formulations for the treatment of UC via the oral route, considering its ease of administration and high patient acceptance. In most cases, drug release is triggered by pH or bacterial degradation. However, these characteristics can vary significantly among IBD patients, potentially compromising treatment efficacy. The development of targeted delivery systems for the treatment of CD presents greater challenges, as the inflammation can affect any section of the GI tract. Depending on the location of the inflammation and severity of the disease, parenteral or rectal drug administration may be preferred. However, there is a noticeable gap in the development of nano-based formulations for these administration routes. Regarding rectal dosage forms, patients would benefit from formulations with enhanced adhesion and mucosal penetration. Composite nanomedicine administered rectally could provide a more uniform delivery from the rectum to the left colon and could optimize retention minimizing side effects. There is still unexplored potential for rectal drug delivery in a localized pathology such as IBD, for which innovative platforms could be developed and used to repurpose drugs with indication for IBD but proven to be unsuitable for oral intake due to adverse events.

Formulation efficacy is primarily evaluated in vivo, mostly in murine models. Even though there are numerous rodent models of IBD currently available (Mizoguchi et al., 2020), chemically induced IBD models such as DSS and TNBS-induced colitis models are most frequently employed. These models promote rapid onset of inflammation and are useful for formulation screening, but they do not represent a model of chronic inflammation. Intestinal fibrosis commonly accompanies IBD, but therapies in development and the animal models applied for their evaluation often overlook this condition. For a comprehensive review of the pathogenesis and therapeutic targets of fibrosis in IBD, we refer the reader to Rieder et al. (2024).

Given the complexity of IBD pathophysiology, accurately mimicking this disease in animal models is challenging. Therefore, there have been intensive efforts to develop reliable in vitro models to complement animal models. 2D cell co-culture models combine Caco-2 cells with HT29-MTX to mimic the mucus layer or with immune cells to simulate an inflamed human intestinal epithelium. Additionally, 3D models have been created to provide a more accurate representation of the intestine's multilayered structure. These include 3D cell co-cultures, intestine-on-a-chip models, and human intestinal organoids. For a comprehensive review of 3D models of IBD, we refer the reader to Ferreira et al. (2024).

In conclusion, we stress the importance of combining cell-based in vitro models and appropriate animal models to evaluate the efficacy and safety of new drug formulations.

AUTHOR CONTRIBUTIONS

Rafaela Gazzi: Conceptualization (lead); writing – original draft (lead); writing – review and editing (lead). **Rita Gelli:** Conceptualization (supporting); writing – original draft (lead); writing – review and editing (supporting). **Simone Aleandri:** Writing – original draft (lead); writing – review and editing (supporting). **Marianna Carone:** Writing – original draft (supporting); writing – review and editing (supporting). **Paola Luciani:** Conceptualization (lead); funding acquisition (lead); project administration (lead); resources (lead); writing – original draft (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

Patent pending for the TIF-Gel technology. *Patent applicants*: University of Bern and University of Zurich. *Name of inventor(s)*: Marianna Carone, Marianne R. Spalinger, Robert A. Gaultney, Rafaela Gazzi, Philippe Krebs, Gerhard Rogler, Paola Luciani, Simone Aleandri. *Application number*: International Patent Application No. PCT/EP2023/076606. Filing Date: 26.09.2023. P.L. has consulted and received research funding from Lipoid GmbH, Sanofi-Aventis Deutschland and DSM Nutritional Products Ltd. and has received research funding from PPM Services AG.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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