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Therapeutic systems based on natural gut microbiota modulators: the latest advances in the treatment of inflammatory bowel disease

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The gut microbiota plays an indispensable role in maintaining gut health. However, the imbalance of gut microbiota under inflammatory conditions is closely related to the acceleration of inflammatory bowel disease (IBD) progression. Consequently, modulating the gut microbiota is one of the crucial strategies for treating IBD. Naturally sourced phytonutrients, probiotics, prebiotics, gut microbiota metabolites and extracellular vesicles (EVs) exhibit remarkable gut microbiota regulation capabilities through diverse pathways, for instance, exerting anti-inflammatory and antioxidant activities, competing with harmful bacteria for nutrients, selectively promoting the proliferation of beneficial bacteria, regulating immune homeostasis, and so on. Since they are all derived from nature and exhibit excellent gut microbiota modulation capabilities, we define them as "natural gut microbiota modulators" (NGMMs). In recent years, the thriving development of therapeutic systems has illuminated the direction for the advancement of NGMMs. Constructing therapeutic systems based on MGMMs can overcome the challenges they face in treating IBD and significantly enhance their therapeutic efficacy. In this review, We first reviewed the role of gut microbiota in IBD, and then systematically summarized how the therapeutic system based on NGMMs positively influences the intestinal microbiota. Furthermore, we sort out the challenges faced by these therapeutic systems and offer insights into their prospects.

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1 Introduction

Inflammatory bowel disease (IBD) is a chronic, non-specific inflammatory disease that includes Crohn's disease (CD) and ulcerative colitis (UC).[1] Approximately 7 million people globally are affected by IBD, and over the past three decades, the incidence of IBD has soared in low-income and middle-income countries.[2] Clinical symptoms of IBD include abdominal pain, diarrhoea, blood in the stool, and weight loss.[3] The pathogenesis of IBD is intricate, involving multiple factors such as genetic factors, environmental factors (including air pollution, geography, *etc.*), lifestyle factors (for example, smoking and diet), and gut microbiota imbalance.[4] The fundamental goal of IBD treatment is to restore intestinal epithelial tissue and reshape intestinal homeostasis. At present, the clinical treatment drugs for IBD primarily consist of aminosalicylates, corticosteroids, immunosuppressants, and so on. These drugs can alleviate inflammation, but their efficacy in restoring the tissue and structure of the intestinal epithelium is limited, and long-term use often results in significant side effects.[5,6] Therefore, it is necessary to explore more effective treatment strategies.

The gut microbiota encompasses a complex microbial community, including approximately 160 major bacterial species alongside fungi, parasites, viruses, archaea, and protozoa, all coexisting with the host in an intricate yet stable ecological balance.[7–9] In physiological conditions, the gut microbiota serves as an integral part of the intestinal ecosystem, engaging in a mutually beneficial and symbiotic relationship with the host, and extensively participating in various life activities.[10] However, under inflammatory conditions, the gut microbiota exhibits a state of dysbiosis, characterized by changes in its composition and metabolic disorders, leading to the impairment of its normal functions and exacerbating the progression of inflammation.[11] For example, under the intestinal inflammation condition, the decreased abundance of *Faecalibacterium*, *Phascolarctobacterium*, and *Clostridia clades* IV and XIVa impairs their ability to produce butyrate, utilize hydrogen, and exert other anti-inflammatory properties.[12] In addition, due to the disruption of the intestinal mucosal barrier caused by IBD,

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Clostridium difficile is more likely to colonize and overgrow in the intestine, producing protein toxins that are associated with the destruction of tight junction proteins (TJs), epithelial cell death, and mucosal inflammation.[13,14] Gut microbiota dysbiosis is a crucial factor contributing to the disruption of intestinal homeostasis and intestinal epithelial tissue damage. Modulating the gut microbiota is considered a potential target for the treatment of IBD.[15]

Naturally sourced phytonutrients,[16] probiotics,[17] prebiotics,[11] gut microbiota metabolites,[18] and extracellular vesicles (EVs)[19] demonstrate remarkable abilities to regulate gut microbiota through various pathways. Phytonutrients can exert anti-inflammatory and antioxidant activities to regulate the intestinal microenvironment, thereby restoring the homeostasis of gut microbiota.[20] Supplementing probiotics can inhibit the growth and reproduction of harmful bacteria by competing with them for nutrients, thereby improving the gut microbiota.[21] Prebiotics can selectively promote the proliferation of beneficial bacteria in the gut to regulate the gut microbiota.[22] Gut microbiota metabolites can function as signaling molecules that impact intestinal immune homeostasis and epithelial barrier function, subsequently leading to the improvement of the gut microbiota.[23] EVs can restore the homeostasis of the intestinal microenvironment by directly conducting information transfer with the host's intestinal flora.[24] Since phytonutrients, probiotics, prebiotics, gut microbiota metabolites, and EVs all originate from nature and demonstrate remarkable abilities in regulating the gut microbiota, we define them as ''natural gut microbiota modulators'' (NGMMs), which, due to their wide range of sources and ease of access, confer unique advantages in the treatment of IBD.

However, there are still some issues that arise when using NGMMs to modulate the gut microbiota. The efficacy of phytonutrients is mainly limited by their stability and solubility.[25] For probiotics, the complex digestive tract environment and long transit time can affect their survival rate and colonization rate, thereby impacting their efficacy.[26] Some prebiotics, due to their rapid fermentation characteristics, may lead to a shortage of fermentable carbohydrates for bacteria in the distal colon.[27] Some gut microbiota metabolites have limited efficacy due to their rapid metabolism and excretion in the body.[28] Hence, how to solve these problems to make them better play the regulatory role of intestinal flora has become the focus of our attention. The vigorous development of therapeutic systems offers possible solutions.[29,30] Modifying or encapsulating drug molecules with chemical or biological materials of different properties to construct therapeutic systems can enhance their bioavailability and ensure better therapeutic efficacy.[31–33] From this perspective, they can all be encapsulated and modified to construct therapeutic systems that enable them to better exert their therapeutic effects. In this review, from the perspective of natural sources, we summarize how therapeutic systems based on NGMMs with excellent gut microbiota modulation capabilities address the challenges and limitations they face in practical applications. Furthermore, some therapies related to NGMMs, such as fecal microbiota transplantation (FMT) and synbiotics, have also been summarized. Finally, we will separately summarize and elaborate on the current challenges and prospects of these therapeutic systems.

2 Gut microbiota and IBD

The human gut is home to many microorganisms, which are more than 10 times more numerous than the total number of human cells.[34] And the number of bacteria accounts for more than 90% of the intestinal microorganisms. The gut provides a rich nutrient environment for bacteria to grow, so nearly 100 trillion species of bacteria can exist and colonize the gastrointestinal tract of the human body. Healthy intestinal bacteria consist mainly of *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*, in which *Firmicutes* are dominant (50–75%), followed by *Bacteroidetes* (10–50%), *Actinobacteria* (1–10%), and *Proteobacteria* (usually less than 1%). The gut microbiota is mainly composed of these four phyla and is in dynamic equilibrium under healthy conditions, but the gut microbiota exhibits temporal and spatial differences at the genus level and even more subdivided species levels. From the esophagus distally to the rectum, the number of bacteria varies significantly, with about 10^1 bacteria per gram of content in the esophagus and stomach, and about 10^{12} bacteria per gram of content in the rectum.[35] These gut microbiota can play a significant role in various physiological processes within the host, including substance metabolism, the maintenance of immune homeostasis, and endocrine regulation, thereby influencing the overall gut health of the host.[36] The gut microbiota can break down and ferment certain food components that are difficult for the human body to digest, such as cellulose and some complex carbohydrates, converting them into short-chain fatty acids (SCFAs). This not only provides nutrition for intestinal cells, maintains the integrity of the intestinal mucosa, but also contributes to overall energy metabolism.[37] The homeostasis of the immune system is crucial for intestinal health. Metabolites derived from gut microbiota influence excessive immune cell responses, including those of T cells, B cells, dendritic cells, and macrophages, to maintain immune homeostasis.[38] Furthermore, in situations where nutrients are insufficient, the gut microbiota can compete with pathogenic bacteria for nutrients, thereby restricting the growth and reproduction of the latter and maintaining intestinal health.[39] In return, the gut microbiota can obtain the necessary nutrients from the host to sustain their growth and reproduction. Under normal physiological conditions, the host and gut microbiota form a mutually influencing and interdependent relationship.

However, under pathological conditions, the interdependent relationship between the gut microbiota and the host is disrupted, leading to an unhealthy symbiotic state. Extensive tissue inflammation of the intestinal epithelium leads to the loss of the basis for gut microbiota colonization in the intestine, resulting in a dramatic decrease in gut microbiota, and a significant reduction in diversity.[40] The dysregulation of gut microbiota is closely related to the occurrence of IBD.

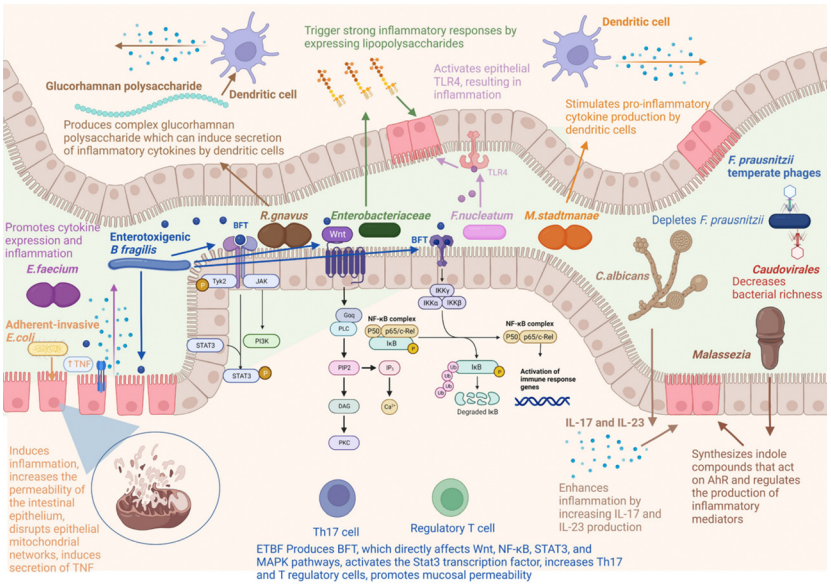

Fig. 1 Microbes involved in inflammatory bowel disease and their molecular mechanisms. *B. fragilis*, *Bacteroides fragilis*; *E. faecium*, *Enterococcus faecium*; *E. coli*, *Escherichia coli*; *F. nucleatum*, *Fusobacterium nucleatum*; *F. prausnitzii*, *Faecalibacterium prausnitzii*; *M. stadtmanae*, *Methanosphaera stadtmanae*; *R. gnavus*, *Ruminococcus gnavus*; TLR4, Toll-like receptor 4; BFT, *B. fragilis* toxin; TNF, tumor necrosis factor; ETBF, enterotoxigenic *B. fragilis*; AhR, aryl hydrocarbon receptor; IL, interleukin; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C. Reproduced from reference [H. Pandey, D. Jain, D. W. T. Tang, S. H. Wong and D. Lal, Gut microbiota in pathophysiology, diagnosis, and therapeutics of inflammatory bowel disease, *Intest. Res.*, 2024, **22**(1), 15–43] with permission from [Korean Association for the Study of Intestinal Diseases], copyright [2024].

Fig. 1 summarizes the gut microbiota associated with the development and progression of IBD, as well as the related molecular mechanisms.[41] Due to the decreased abundance of the intestinal symbiotic flora, the loss of competition and antagonism against pathogenic bacteria provides an opportunity for the colonization of pathogens, leading to an overall shift in the gut microbiota characterized by a reduction in beneficial bacteria and an increase in harmful bacteria.[42] *Fusobacterium* mainly resides in the oral cavity and intestine. Compared with the healthy control group, the abundance of *Fusobacterium* in the colonic mucosa of UC patients is higher. *Fusobacterium varium* can cause colonic mucosal inflammation, exacerbating IBD.[43] Furthermore, due to the disruption of redox homeostasis in an inflammatory state, there is a surge in ROS/RNS levels. ROS/RNS provides terminal electron acceptors for anaerobic respiration, leading to a significant proliferation of facultative anaerobes and a decrease in the abundance of obligate anaerobes.[44] *E. coli* is a Gram-negative, facultative anaerobic bacterium. Evidence shows that the abundance of Adherent-invasive *E. coli* (AIEC) strains increases in the inflammatory state, and AIEC can adhere to and penetrate the intestinal mucosa of patients with IBD, thereby inducing inflammation and increasing the permeability of intestinal epithelium.[45] The decrease in the abundance of beneficial bacteria and the increase in harmful bacteria within the gut microbiota can lead to metabolic disorders, which are manifested primarily by the reduction of beneficial metabolites and the elevation of harmful metabolites.[46,47] The overall level of SCFAs in the intestines of patients with IBD is significantly reduced, mainly attributed to the reduced number of bacteria that produce SCFAs, including *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, and *Dialister invisus*.[18,48] Intestinal microbiota can metabolize tryptophan into indole compounds, which are ligands for the aryl hydrocarbon receptor (AhR). These indole metabolites promote the maturation of Treg cells by activating the AhR, thereby maintaining immune homeostasis. Imbalances in intestinal microbiota metabolism can directly lead to a reduction in the production of indole metabolites, disrupting intestinal immune homeostasis and further exacerbating inflammation.[49] For example, *Clostridium sporogenes* not only metabolize Trp to produce indole-3-acetic acid (IAA) and indole-3-propionic acid (IPA), but they also possess the capability to decarboxylate Trp, resulting in the production of the neurotransmitter serotonin.[50] However, as a symbiotic bacterium, the abundance of *Clostridium sporogenes* can be affected by inflammatory states. On the contrary, some "harmful" gut microbiota metabolites, particularly niacin, taurine, and acylcarnitines, are more abundant in patients with IBD.[48] And taurine has been identified as an activator of mucosal inflammasomes, capable of exacerbating the progression of inflammation.[51] In conclusion, the disruption of gut microbiota is closely related to the development of IBD. Modulating the gut microbiota not only competitively inhibits harmful bacteria by increasing the abundance of beneficial bacteria, thereby reducing the levels of harmful products and inhibiting the spread of inflammation, but also restores the normal function of the gut microbiota to promote the repair of the intestinal epithelial barrier, and maintain immune homeostasis. Therefore, modulating the gut microbiota to restore its homeostasis holds significant importance for the treatment of IBD.

3 Therapeutic systems based on NGMMs

With the continuous exploration of researchers, the NGMMs are found to play a significant role in regulating gut microbiota, and their wide range of sources and ease of access make them promising candidates for the treatment of IBD.[16,52,53] Additionally, many articles have reported that therapeutic systems based on NGMMs are capable of addressing challenges encountered in their applications, thereby enhancing their remarkable abilities to regulate gut microbiota. For example, therapeutic systems with gastric acid resistance can carry phytonutrients through the harsh gastric acid environment and release them precisely at the site of colonic inflammation, thereby improving their bioavailability. Probiotics modified with encapsulation materials or through genetic editing techniques can enhance their adhesion to the intestinal wall, thereby improving their survival and colonization rates within the gut. Therapeutic systems with sustained-release functions can carry prebiotics to extend their fermentation time at the site of colonic inflammation. Therapeutic systems with controlled-release functions can carry indole derivatives to prevent their premature absorption in the small intestine. Extracellular vesicles themselves constitute a therapeutic system containing multiple components, capable of providing nutrients to intestinal microbiota to promote their growth and reproduction. In Fig. 2, We summarized the therapeutic systems based on NGMMs and in this section, we will delve into the specifics of NGMMs and the therapeutic systems based on them, how function to modulate gut microbiota for the treatment of IBD.

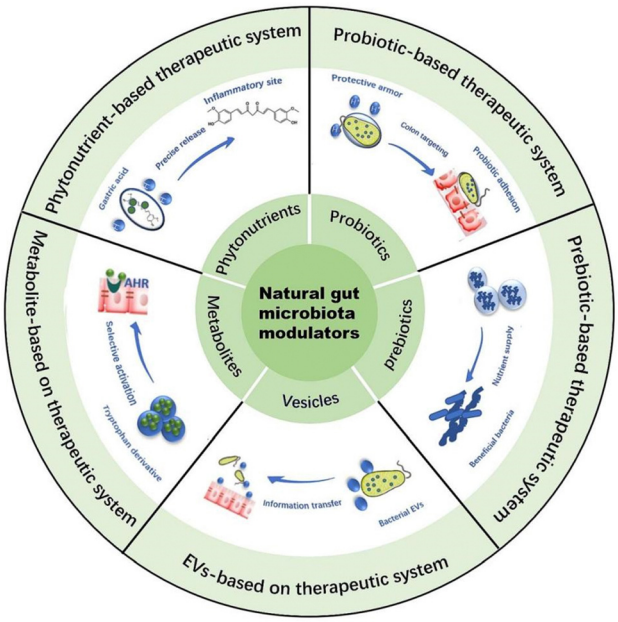

Fig. 2 The therapeutic systems based on natural gut microbiota modulators for IBD treatment. EVs: extracellular vesicles; metabolites: gut microbiota metabolites; the phytonutrients-based therapeutic system enhances their bioavailability and achieves responsive release at sites of intestinal inflammation. The probiotic-based therapeutic system provides armor for probiotics to overcome the gastric acid environment, thereby improving their survival and colonization rates. The prebiotic-based therapeutic system selectively supplies nutrients to beneficial bacteria to promote their proliferation. The extracellular vesicles (EVs)-based therapeutic system facilitates information transfer between the host and gut microbiota to regulate the homeostasis of the gut flora. The gut microbiota metabolites-based therapeutic system selectively activates relevant immune pathways to maintain immune homeostasis.

3.1 Phytonutrient-based therapeutic systems

Phytonutrients, also known as nutraceutical plant chemicals, are secondary metabolites accumulated in different parts of plants.[16] Based on their unique properties and different structures, phytonutrients are classified into phenolic acids, flavonoids, carotenoids, tocopherols, curcuminoids, and so on.[54] Due to their excellent anti-inflammatory,[55] antioxidant,[56] and immune-modulating activities,[57] significant progress has been made in the treatment of IBD by using phytonutrients.[58] For example, epigallocatechin-3-gallate (EGCG), which is abundant in tea, can treat IBD by stabilizing mast cells and inhibiting pro-inflammatory cytokines such as IL-6, monocyte chemoattractant protein-1 (MCP-1), and TNF-α through the NF-κB pathway.[59,60] With the continuous deepening of research on the treatment of IBD using phytonutrients, many researchers have shifted their focus to the gut microbiota regulating the activity of phytonutrients. In Table 1, we have summarized some phytonutrients that can regulate the gut microbiota. For example, chlorogenic acid (CGA), a common phenolic acid found in coffee and tea, exhibits excellent therapeutic effects on IBD. CGA is capable of reversing the decrease in intestinal microbial diversity caused by dextran sulfate sodium (DSS) and also increasing the relative abundance of *Lactobacillus*.[61] However, the therapeutic effects of phytonutrients are often affected by their stability and bioavailability.[62] How to improve the bioavailability and stability of phytonutrients to better exert their gut microbiota-modulating capabilities has become our focus of attention. Based on this, many therapeutic systems have been developed to deliver phytonutrients to the intestinal inflammation site to better exert their therapeutic effects. Next, therapeutic systems will be categorized based on the structures of various phytonutrients, with an elaboration on how they exert their gut microbiota modulating effects.

3.1.1 Phenolic acids. Phenolic acids are compounds that contain a large number of phenol rings and carboxyl groups. Dietary phenolic acids have been proven to improve intestinal function by reducing intestinal inflammation and altering gut microbiota.[61] Ferulic acid (4-hydroxy-3-methoxycinnamic acid; FA) possesses excellent anti-inflammatory and antioxidant activities and is widely found in symbionts, grasses, grains, fruits, and other sources.[79,80] As a hydrophobic small molecule drug, ferulic acid exhibits low bioavailability during delivery through the gastrointestinal tract. Chengke Zhao *et al.* synthesized lignin-like polymers (FAL) through the free radical polymerization of FA subsequently, the FAL underwent self-assembly to form FAL nanoparticles (FAL NPs). Since the inherent weakly acidic groups in FA remain stable under strongly acidic conditions and can dissociate under alkaline

Table 1 Phytonutrients with the ability to regulate gut microbiota

		Alterations of gut microbiota		
Category	Name	Bacteria with increased abundance	Bacteria with decreased abundance	Ref.
Phenolic acids	Chlorogenic acid	*Ruminococcaceae*, *Lactobacillaceae*, *Bacteroidaceaee*, *Erysipelotrichaceae* ↑	*Firmicutes: Bacteroides*, *Desulfovibrionaceae* ↓	63
	Protocatechuic acid	*Bifidobacterium*, *Olsenella*, *Rikenella*, *Turicibacter, Clostridium_sensu_stricto* ↑	*Lactococcus*, *Enterorhabdus* ↓	64
	Caffeic acid	*Bifidobacterium*, *Actinobacteria* ↑	*Firmicutes: Bacteroides*, *Romboutsia*, *Lactobacillus*, *Clostridium_sensu_stricto* 1 ↓	65
	p-Coumaric acid	*Candidatus saccharimonas*, *Clostridium sensu stricto*, *Leuconostoc*, *Gastranaerophilales*↑	*Morganella*, *Holdemanella*, *Fusicatenibacter*, *Serratia*↓	66
Flavonoids	Quercetin	*Bacteroides*, *Bifidobacterium*, *Lactobacillus*, *Clostridia* ↑	*Fusobacterium*, *Enterococcusin*↓	67
	Tangeretin	*Lachnospiraceae*, *Lactobacillaceae* ↑	*Enterobacteriaceae*, *Alistipes*↓	68
	Rutin	*Verrucomicrobia*, *Roseburia*, *Bacteroides*, *Alistipes*, *Parasutterella*, *Akkermansia* ↑	*Lachnospiraceae*, *Ruminococcaceae*, *Erysipelotrichaceae*↓	69
	Luteolin	*Proteobacteria*, *Lactobacillus*, *Bifidobacterium*, *Desulfovibrio* ↑	*Firmicutes to Bacteroides*, *Actinobacteria*↓	70
Carotenoids	β-Carotene	*Firmicutes*, *Actinobacteria*, *Faecalibacterium*, *Candidatus stoquefichus*, *Akkermansia* ↑	*Bacteroidetes*, *Proteobacteria*↓	71 and 72
	Lycopene	*Firmicutes*, *Actinobacteria*, *Lactobacillus*, *Clostridiales*, *Bifidobacterium*, *Lachnospiraceae* ↑	*Proteobacteria*, *Mucispirillum*↓	73
	Astaxanthin	*Lactobacillus*, *Bifidobacteria* ↑	*Enterobacteriaceae* spp., *Clostridium coccoides* ↓	74
	Fucoxanthin	*Lachnospiraceae* ↑	*Bacteroidales*, *Rikenellaceae*↓	75
Tocopherols	α-Tocopherol	*Bacteroides acidifaciens*, *Roseburia* ↑	*Parabacteroides goldsteinii*, CL02T12C30↓	76
	γ-Tocopherol	*Bifidobacterium*, *Roseburia* ↑	*Candidatus Saccharimonas*↓	77
Curcuminoids	Curcumin	*Bacteroidetes*, *Muribaculaceae* ↑	*Deinococcus-Thermus*, *Bacteroides*, *Ruminococcaceae* ↓	78

conditions, the pH sensitivity of FAL NPs enables them to withstand the highly acidic gastric environment (pH 0.9–3.5) and ensures precise release of FA at intestinal inflammatory sites, significantly enhancing its bioavailability. After oral administration, FAL NPs can effectively scavenge ROS to reduce intestinal mucosa damage induced by oxidative stress, weaken local immune responses, and ultimately alleviate inflammation. Furthermore, during this process, the gut microbiota is also improved. The *Enterobacteriaceae* can lead to a reduction in bacterial diversity and enhanced expression of pro-inflammatory cytokines, such as TNF-α. *Lactobacillus* is a probiotic associated with regulating inflammatory cytokines and inducing regulatory T cells. FALNPs significantly reduced the abundance of *Enterobacteriaceae* and increased the number of *Lactobacillus*, thereby promoting the recovery of colonic inflammation.[81]

3.1.2 Flavonoids. The flavonoids are a class of 2-phenylchromene compounds that possess a C6–C3–C6 basic carbon skeleton.[82] Quercetin (QCT) is a common flavonoid found in fruits, vegetables, and red onions, existing in the forms of glycosides and aglycones. It can reduce inflammation and pyroptosis induced by LPS through the TLR4/NF-κB/NLRP3 pathway.[83,84] However, the poor chemical stability of quercetin leads to its low bioavailability. Lechen Wang *et al.* encapsulated QCT within *N*-succinyl chitosan (NSC) by crosslinking it with sodium alginate (SA) to construct QCT nanoparticles (QCT NPs). The *in vitro* release experiment demonstrated that QCT NPs exhibited the highest cumulative release rate in a pH 7.4 medium, with a release amount reaching 77%, whereas in a pH 1.2 medium, the release rate was the lowest, with a release amount only reaching 24%. The carboxyl groups of sodium alginate ensure that the QCT NPs can withstand the acidic environment of the stomach, contracting at low pH and dissolving at higher pH, enabling them to reach the site of intestinal inflammation and release QCT in the weakly alkaline environment which effectively enhances the bioavailability of QCT and significantly improves its therapeutic effects. QCT NPs are capable of reducing the expression of inflammatory cytokines in mice with colitis, alleviating colonic inflammatory infiltration, increasing goblet cell density and mucin proteins, and effectively restoring intestinal epithelial barrier (IEB). *Akkermansia muciniphila* is a Gram-negative anaerobic mucus-layer-degrading bacterium and its metabolites have a positive regulatory effect on the intestinal immune system.[85] After the administration of QCT NPs, the relative abundance of *Akkermansia* and *Lactobacillus* increased significantly. Moreover, the levels of short-chain fatty acids were significantly increased after QCT NPs treatment.[86]

3.1.3 Carotenoids. Carotenoids are a class of natural liposoluble pigments that possess an isoprenoid-like structure.[87] Astaxanthin (AST) as a type of carotenoid, has attracted much attention due to its great potential in the treatment of IBD. However, AST is a highly unsaturated molecule, which leads to its tendency to degrade when exposed to acidic pH, certain enzymes, oxygen, and light, limiting its therapeutic effects.[88] Xiumin Zhang *et al.* modified triphenylphosphine (TPP) with cysteine (Cys) and then assembled it into an intelligent polymeric nanocarrier through an EGCG-mediated Mannich reaction (EGCG-Cys-TPP) for the efficient delivery of AST. EGCG-Cys-TPP can protect the structural stability of astaxanthin during gastrointestinal transport, and after reaching the inflammatory site,

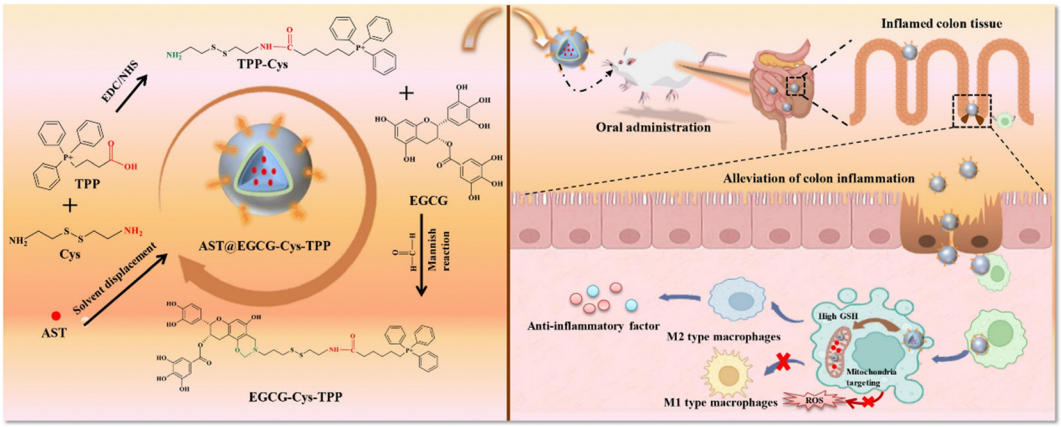

Fig. 3 Schematic illustration of the formation of a dual nutrition nanocarrier oral delivery system for mitochondria targeting and GSH response (left) and its intervention effect on the IBD model (right). Reprinted from X. Zhang, W. Su and Y. Chen *et al.*, Bi-functional astaxanthin macromolecular nanocarriers to alleviate dextran sodium sulfate-induced inflammatory bowel disease, *Int. J. Biol. Macromol.*, **256**, 128494, Copyright (2024), with permission from Elsevier.

the responsiveness of Cys to GSH can ensure the release of AXT. *In vitro* studies have demonstrated that AXT@EGCG-Cys-TPP exhibits enhanced mitochondrial accumulation tendencies, leading to the effective elimination of reactive oxygen species (ROS) and preservation of optimal mitochondrial membrane potential, which is approximately 1.5 times that of free AST and EGCG. Importantly, *in vivo* experiments have shown that the colon length of IBD mice treated with these nanocarriers increased by 51.29%, and promoted the polarization of M2 macrophages. The gut microbiota has been greatly improved in mice with DSS-induced colitis after AXT@EGCG-Cys-TPP treatment (Fig. 3).[89]

3.1.4 Tocopherols. Tocopherols are the natural forms of vitamin E, which encompass α-, γ-, and δ-tocopherol (αT, γT, and δT), possessing antioxidant and anti-inflammatory properties.[90] These compounds have been demonstrated to exert protective effects on intestinal health. *Roseburia intestinalis* is an anaerobic, Gram-positive, slightly curved rod-shaped flagellated bacterium that produces butyrate in the colon, which has been proven to prevent intestinal inflammation and maintain energy homeostasis by producing metabolites.[91] Supplementation with γ-tocopherol-rich tocopherols (γTmT) significantly reduced the depletion of *Roseburia* relative abundance induced by DSS. *Bacteroides acidifaciens*, as a new generation of probiotics, has demonstrated therapeutic effects on IBD.[92] The addition of α-tocopherol increased the relative abundance of *Bacteroides acidifaciens* under DSS conditions.[76] α-tocopherol is a lipophilic antioxidant. M. Plaza-Oliver *et al.* constructed a nanoemulsion as a new oral nanocarrier (NE-ADP) by stabilizing α-tocopherol with ascorbyl-2,6-dipalmitate.[93] NE-ADP exhibits good stability in gastrointestinal media, and NE and ADP work synergistically to exert antioxidant effects for the treatment of IBD.

3.1.5 Curcuminoids. Curcuminoids are a class of chemical compounds known as diarylheptanoids, which primarily encompass curcumin, demethoxycurcumin, and bisdemethoxycurcumin.[94] Curcumin (Cur) exhibits strong antioxidant activity and regulatory effect on the gut microbiota, which is mainly manifested in its ability to increase the abundance and diversity of gut microbiota in mice with DSS-induced colitis, as well as its capacity to correct the relative abundance of *Bacteroidetes* altered by DSS.[78] However, the poor solubility of Cur in water, photodegradation, and chemical instability limit its direct application in the treatment of IBD. Jintao Li *et al.* constructed a metal polyphenol network (MPN) *via* metal coordination between epigallocatechin gallate (EGCG) and Fe^{3+} and encapsulated Cur into MPN to generate Cur-MPN. Cur-MPN can effectively scavenge ROS. Then, the Cur-MPN is encapsulated within the yeast microcapsules (YM) to obtain CM@YM CM@YM is capable of protecting Cur-MPN from harsh gastrointestinal environments and enhancing its targeting and retention capabilities in inflamed colons. When orally administered, CM@YM can alleviate DSS-induced colitis by scavenging ROS, reducing pro-inflammatory cytokines, exhibiting both protective and therapeutic effects, thereby restoring barrier function and maintaining intestinal homeostasis. Importantly, CM@YM also regulates the gut microbiota to a beneficial state by improving bacterial diversity, shifting the composition to an anti-inflammatory phenotype, and increasing the content of short-chain fatty acids (SCFAs) such as acetic acid, propionic acid, and butyric acid (Fig. 4).[95]

In summary, phytonutrients hold immense potential in regulating gut microbiota for the treatment of IBD. However, due to their inherent properties, including hydrophobicity, poor chemical stability, susceptibility to oxidation, and photolysis, they cannot fully exert their therapeutic effects and regulatory role on gut microbiota. By constructing a therapeutic system to load phytonutrients, their bioavailability can be greatly enhanced and precise release at the site of pathology ensured, thereby maximizing their therapeutic benefits.

3.2 Probiotic-based therapeutic systems

Minor changes in gut microbiota can trigger fluctuations in intestinal homeostasis, causing a "butterfly effect" and leading to severe inflammatory reactions. Probiotics can be regarded as

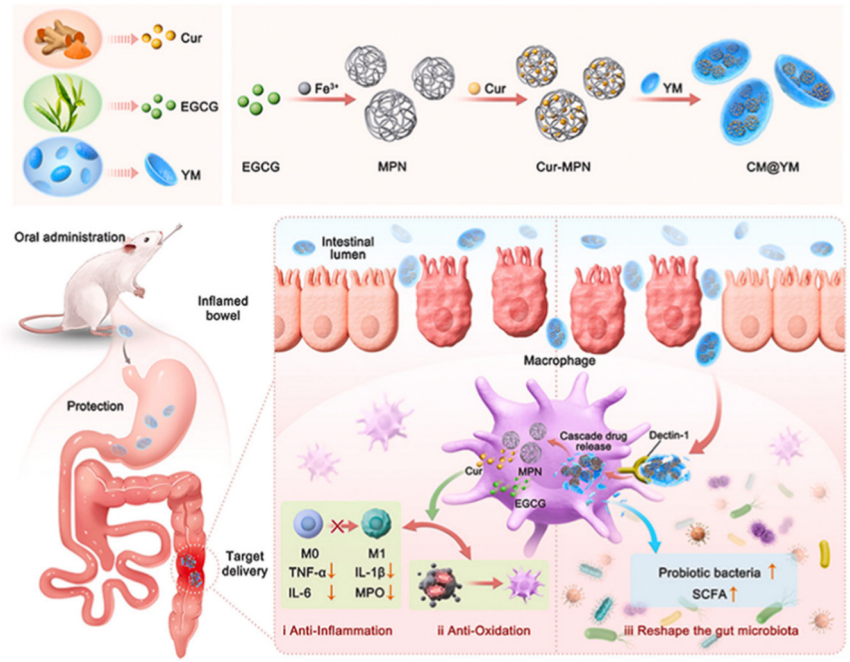

Fig. 4 Schematic illustration of preparation and potential therapeutic mechanisms of CM@YM. Curcumin was self-assembled into the MPN formed by the coordination of EGCG and Fe^{3+} to form the ROS scavenger Cur-MPN, which was then encapsulated in YM by chemical precipitation to obtain CM@YM. Reprinted from J. T. Li, J. Song and Z. C. Deng *et al.*, Robust reactive oxygen species modulator hitchhiking yeast microcapsules for colitis alleviation by trilogically intestinal microenvironment renovation, *Bioact. Mater.*, **36**, 203–220, Copyright (2024), with permission from Elsevier.

the "fulcrum of Archimedes", used to leverage the disrupted state of gut microbiota under inflammatory conditions and improve the composition of gut microbiota.[17] FAO (Food and Agriculture Organization of the United Nations) and WHO (World Health Organization) define probiotics as live microorganisms that confer a health benefit on the host when administered in adequate amounts.[96] This means that the vitality and quantity of probiotics will determine the extent to which they can influence the gut microbiota. However, in practice, the direct consumption of probiotics often yields suboptimal results due to their low survival and colonization rates in the intestine. This can be attributed to two main factors: physiological and pathological. Physiological factors refer to the fact that before probiotics reach the site of colonic inflammation, they must first pass through the digestive tract.[97] The complex physiological environment of the digestive tract and the long duration of passage can both affect the viability of probiotics.[98] Pathological factors refer to the loss of mucus layer in the intestinal tract during inflammatory states, which causes probiotics to lose their colonization sites, resulting in a low colonization rate.[99] How to effectively enhance the survival rate of probiotics and their colonization rate at the site of intestinal inflammation is a crucial point in probiotic-mediated regulation of gut microbiota. To address this challenge, many researchers have developed therapeutic systems by encapsulating probiotics with protective layers to enhance their survival and colonization rates. We refer to these as exogenously modified probiotic therapeutic systems. Furthermore, the rapid advancement of gene engineering technology has opened up another pathway to enhance the therapeutic efficacy of probiotics by equipping them with new traits through gene editing techniques to cope with complex environmental conditions. We refer to this as the endogenously modified probiotic therapeutic system. In this section, we will provide detailed introductions to these two types of therapeutic systems.

3.2.1 Exogenous modified probiotic therapeutic systems. Using exogenous materials to modify or encapsulate probiotics to construct a therapeutic system, thereby enhancing their survival ability and colonization rate, is an effective method for treating IBD.[100] During the process of exogenous encapsulation, the probiotic, as part of the therapeutic system, is modified to acquire the ability to resist complex lesion environments without compromising its vitality.[101] The modification coatings for probiotics encompass metal–polyphenol networks (MPNs), polymers, polysaccharides, proteins, biofilms, and so on. These various modification materials can endow probiotics with different exogenous functions, such as immunoregulation, antioxidant properties, and anti-inflammatory characteristics, paving the way for better colonization of probiotics and enabling them to exert their regulatory role in the intestinal flora.[102] We will classify these therapeutic systems based on the modification materials and provide detailed introductions to each. In Table 2, we summarized the encapsulation materials, encapsulation processes, and their impacts on gut microbiota for both probiotic therapeutic systems based on exogenous modification.

3.2.1.1 MPN-modified prebiotic therapeutic systems. MPNs are supramolecular network structures consisting of metal ions coordinated to phenolic ligands.[112] Due to their unique physicochemical properties and biocompatibility, MPNs have

Table 2 Probiotic-based therapeutic systems

Classification	Encapsulation material	Probiotic/core	Encapsulation process	Alterations of gut microbiota	Ref.
MPN-modified probiotic therapeutic systems	Fe^{3+}–tannic acid (Fe–TA) cross-linking network and carboxymethylated β-glucan (mGN)	ECN	Fe–TA network is formed through electrostatic interaction on the ECN surface; mGN is deposited on the Fe–TA network by hydrogen bonding	*Bacteroidetes*, *Bifidobacterium*, SCFAs ↑, *Escherichia Shigella* ↓	103
	Mn^{2+} and polydopamine	Lactic acid bacteria (LAB)	Mn^{2+} released by LAB mediates the oxidation of dopamine on the surface of LAB	—	104
Polymer-derived probiotic therapeutic systems	Nitric oxide (NO)-responsive poly-γ-glutamic acid hydrogel microcapsules (NRPM)	Lactic acid bacteria (LAB)	Using a novel droplet-based microfluidic technology, probiotics are embedded into γ-PGA microgels.	*Turicibacter*, *Acidaminococcaceae*, *Negativicutes*, and *Phascolarctobacterium* ↑	105
Polysaccharide-modified probiotic therapeutic systems	Biocatalytic ferrihydrite nanoparticles and fucoidan-derived protective shield	ECN	One-step bioinspired mineralization process and a layer-by-layer electrostatic selfassembly process	*Muribaculaceae*, *Prevotellaceae* UCG-001, *Lachnospiraceae* NK4A136 ↑, *Proteobacteria*, *Escherichia Shigella* ↓	106
	High-molecular-weight hyaluronan (HMW-HA) and Fe^{3+} and catechins network and	ECN	Layer-by-layer coating procedure	*Lactobacillus*, *Muribaculaceae*, *Parabacteroides* ↑, *Desulfovibrio*, *Clostridium sensu stricto* 1, *Escherichia Shigella* ↓	107
	Hyaluronic acid (HA) Dopamine (DOPA) Phenylboric acid (PA)	*Lactobacillus acidophilus* (Lac)	Lac solution was incubated with HDP solution for 4 h at a speed of 300 rpm (HDP@Lac)	*Lactobacillus acidophilus*, *Akkermansia* ↑, *Desulfovibrionaceae* ↓	108
Protein-modified probiotic therapeutic systems	Proanthocyanidins (PAs), mucin (MUC), phosphatidylcholine (PC) and methacrylate modified gelatin porous microgels	*Akkermansia muciniphila* (AKK)	Modifying AKK with proanthocyanidins (PAs), mucin (MUC), and phosphatidylcholine (PC), and then encapsulating it within methacrylate-modified gelatin porous microgels (AKK@GPMGs)	*Lactobacillaceae*, *Muribaculaceae*, *Akkermansiaceae* ↑, *Enterobacteriaceae*, *Desulfovibrionaceae*, *Porphyromonadaceae* ↓	109
	Ca^{2+}–tannic acid (Fe–TA) cross-linking network and mucin	ECN	Layer-by-layer coating with mucin and TA	*Lachnospiraceae* NK4A136, *Bifidobacterium adolescentis* ↑, *Escherichia coli* ↓	110
Biofilm-modified probiotic therapeutic systems	A self-coating biofilm	*Bacillus subtili* (BS)	By cultivating BS on a solid minimal salt-glucose-glutamate (MSgg) agar plate, a self-coating biofilm formed on the surface of the BS	—	111

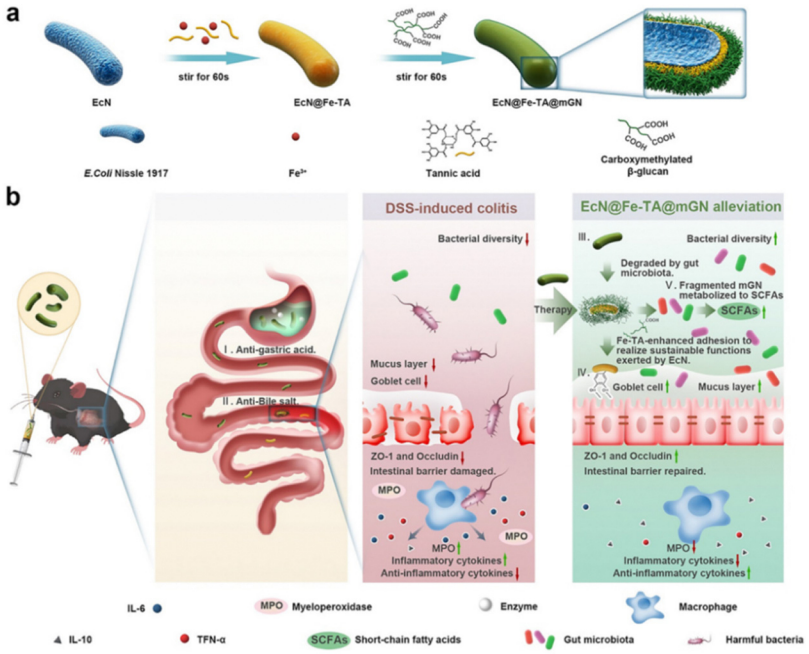

Fig. 5 Schematic illustration of the fabrication of EcN@Fe–TA@mGN and its alleviation process for DSS-induced colitis in mice. (a) Preparation of EcN@Fe–TA@mGN. (b) Probiotics exhibited superior resistance to gastric acids and bile salts after being armed with a Fe–TA@mGN "shield" and remained intact in the upper digestive tract. Reproduced from reference [A. Xie, H. Ji and Z. Liu *et al.*, Modified Prebiotic-Based "Shield" Armed Probiotics with Enhanced Resistance of Gastrointestinal Stresses and Prolonged Intestinal Retention for Synergistic Alleviation of Colitis, *ACS Nano*, 2023, **17**(15), 14775–14791] with permission from [ACS Publictions], copyright [2023].

received considerable attention in the biomedical field in recent years. MPNs, capable of forming continuous and stable coatings on various substrate surfaces and exhibiting remarkable defensive and adhesive properties, hold enormous potential for application in the modification of probiotics.[113] Polyphenols and metal ions can chelate on the surface of probiotics, forming a protective layer that enhances the survival rate of the probiotics. Furthermore, the phenolic hydroxyl groups in MPNs can covalently bind with proteins at sites of colonic inflammation, thereby strengthening the adhesion of probiotics to the intestinal wall.[17] *Escherichia coli* Nissle 1917 a Gram-negative strain, not only exhibits antagonistic effects against a variety of intestinal pathogens but also regulates the secretion of immune factors *in vivo*, enhancing the host's immune capacity.[114] Xie Anqi *et al.* used Fe^{3+}–tannic acid (Fe–TA) cross-linking network and carboxymethylated β-glucan (mGN) to modify *Escherichia coli* Nissle 1917 (ECN) (ECN@Fe–TA@mGN). Under the protection of the Fe–TA@mGN "shield", the survival rate of the armed ECN after simulated gastric juice was 1720 times higher than that of bare EcN. After reaching the colonic inflammatory site, mGN is degraded with the assistance of enzymes secreted by intestinal microorganisms, releasing Fe–TA-modified ECN (ECN@Fe–TA). The Fe–TA network can help ECN adhere to the intestinal inflammatory site, greatly improving the retention rate of ECN at the colonic inflammatory site. The intestinal retention rate of EcN@Fe–TA@mGN reached as high as 47.54 ± 6.06% at 16 hours post-administration, while nearly all of the bare EcN were excreted within 8 hours post-administration. Moreover, EcN@FeTA@mGN is able to positively regulate gut microbiota, thereby alleviating intestinal inflammation (Fig. 5).[103]

3.2.1.2 Polymer-derived probiotic therapeutic systems. Polymers are macromolecules composed of many repeating units connected by covalent bonds, which mainly include natural polymers and synthetic polymers.[115] As an effective drug delivery tool, polymers have shown wide application and clinical success in various diseases due to their simple synthesis methods, the ability to adjust chemical structures and self-assemble hierarchical structures, as well as good biocompatibility and biodegradability.[116] Due to their ability to achieve passive/active targeted delivery, adhesion, mucus penetration, and controlled drug release through their physicochemical properties such as surface charge, surface functional groups, and polymer segments, polymers have emerged as excellent carriers for probiotic delivery.[117] For example, poly-γ-glutamic acid (γ-PGA) is a safe and edible polymer that constitutes the mucus in fermented foods. It has been reported to counteract the colonization of harmful microorganisms in the intestine and possesses excellent anti-inflammatory properties, making it an excellent carrier for probiotic delivery.[118,119] Rui Wang *et al.* constructed nitric oxide (NO)-responsive γ-PGA hydrogel microcapsules (NRPM) based on a microfluidic technology platform for encapsulating lactic acid bacteria (LAB). NPRM demonstrates stability in a gastric acid environment. Due to the cytoprotective effects of NRPM, the modified probiotics exhibited higher viability in simulated gastric (89.67%) and intestinal (93.67%) fluid

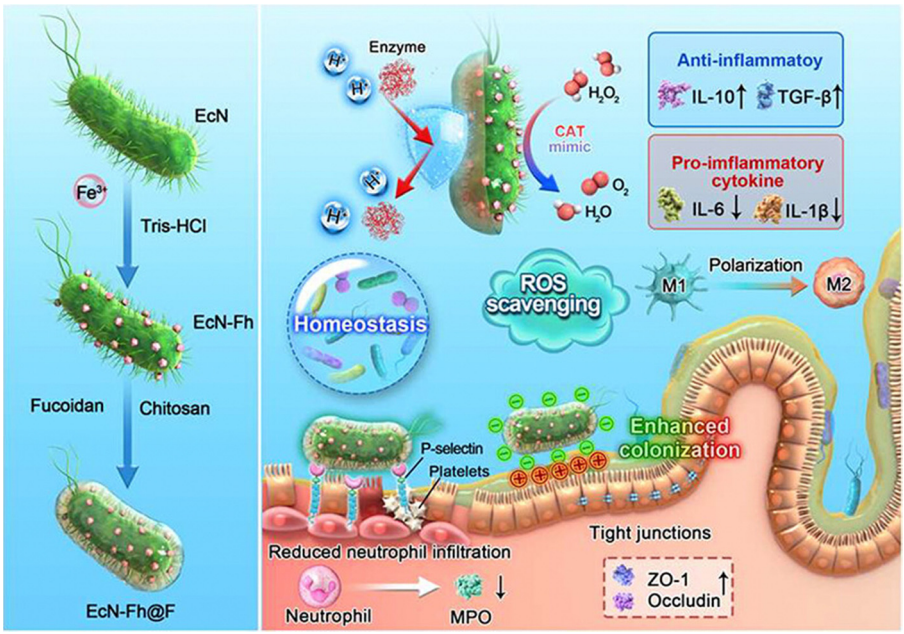

Fig. 6 Schematic illustration of the development of engineered probiotics for multipronged management of IBD and the characterization of EcN-Fh. The *in situ* growth of biocatalytic Fh NPs on probiotics through a one-step bioinspired mineralization process. The Fh NPs-decorated probiotics are further coated with a fucoidan-derived protective shield to enhance colon delivery. Reproduced from reference [T. Chen, W. Meng and Y. Li *et al.*, Probiotics Armed with *In Situ* Mineralized Nanocatalysts and Targeted Biocoatings for Multipronged Treatment of Inflammatory Bowel Disease, *Nano Lett.*, 2024, **24**(24), 7321–7331] with permission from [ACS Publictions], copyright [2024].

environments, compared to 0% and 61.60% for the free cells, respectively. At sites of colonic inflammation, it rapidly releases LAB in response to NO molecule stimulation, facilitating intestinal mucosal repair and regulating the balance of intestinal flora, ultimately achieving the mitigation of colitis.[105]

3.2.1.3 Polysaccharide-modified probiotic therapeutic systems. Polysaccharides are high-molecular-weight carbohydrates very large variety of architecture (linear or branched) and linkages connecting their monomeric units. They are ubiquitous in plants, fungi, microorganisms, algae, and animals.[120,121] Evidence suggests that some polysaccharides exhibit good resistance to gastric acid. In the gastric environment, polysaccharides may undergo a slight or significant reduction in molecular weight, potentially due to the cleavage of glycosidic bonds and dispersion of aggregates. However, they are not digested into monosaccharides for absorption and utilization.[122] This makes them excellent carriers for the delivery of probiotics through the complex gastrointestinal environment. In addition, some polysaccharides exhibit excellent targeting capabilities towards inflamed areas of the colon, ensuring the precise release of the therapeutic system at the site of the lesion. For example, fucoidan is not only a specific ligand for P-selectin, which is overexpressed in inflamed intestines, but it is also capable of electrostatic binding to positively charged proteins accumulated in damaged intestinal epithelia.[123,124] Chen ting *et al.* coated the nanozyme-loaded ECN (ECN-Fh) with fucoidan (ECN-Fh@F) through a layer-by-layer electrostatic self-assembly process using chitosan. This fucoidan-based shielding further encapsulates the probiotics, imparting them with additional inflammatory colon targeting capabilities. Upon oral administration, the engineered probiotics significantly enhanced the viability and colonization of the inflamed gut (Fig. 6).[106] High-molecular-weight hyaluronan (HMW-HA), is a negatively charged glycosaminoglycan biopolymer that specifically binds to the CD44 receptor. Limeng Zhu *et al.* utilized HMW-HA as a nano-armor for ECN, endowing the probiotics with exceptional resistance to various extreme environmental conditions. In the gastric acid environment, the relative survival rate of EcN@PC-Fe/HA was 80.3%, while the relative survival rate of native EcN was 6.0%. The functionalization of HMW-HA, through its specific positive charges associated with inflammatory lesions and the high expression of CD44 receptors, facilitates the targeted accumulation of probiotics in the diseased regions of the gut. Observed through IVIS, the fluorescence signal of EcN-mCherry@PC-Fe/HA towards inflamed colon was 1.6 times that of EcN-mCherry@PC-Fe. Protected by nano-armor, ECN can effectively enhance the diversity of intestinal microbiota and reduce intestinal pathogens.[107] In addition to directly using polysaccharides for probiotic delivery, chemical modification can endow polysaccharides with new properties that make them better suited for probiotic delivery. Qian-Xiao Huang and his colleagues utilized dopamine protected by phenylboric acid to modify hyaluronic acid (HDP) for the delivery of *Lactobacillus acidophilus* (Lac). HDP can protect Lac from the damaging effects of gastric acid, enhancing its survival rate. In the presence of high levels of ROS, the phenylborate ester groups in Lac@HDP undergo oxidation and cleavage, exposing catechol hydroxyl groups and imparting a robust mucosal adhesion capability. This significantly prolongs the retention time of Lac at the inflammatory site.[108]

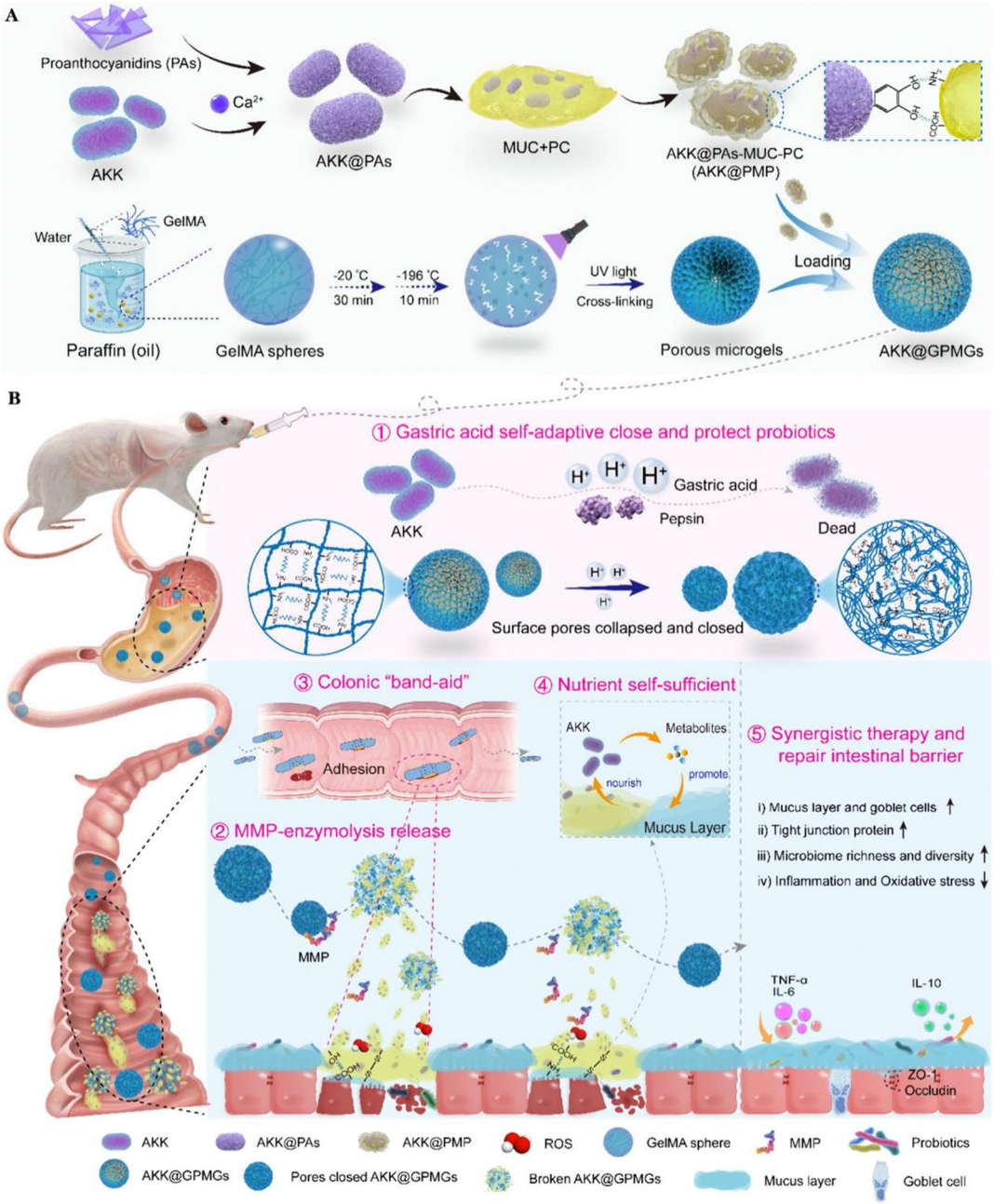

Fig. 7 Gastrointestinal self-adaptive and nutrient self-sufficient Akkermansia muciniphila-gelatin porous microgels (AKK@GPMGs) for synergistic therapy of UC: (A) preparation of AKK@GPMGs; (B) properties and synergistic therapy of AKK@GPMGs. Reproduced from reference [Y. Zhang, Y. Wang and X. Zhang *et al.*, Gastrointestinal Self-Adaptive and Nutrient Self-Sufficient *Akkermansia muciniphila*-Gelatin Porous Microgels for Synergistic Therapy of Ulcerative Colitis, *ACS Nano*, 2024, **18**(39), 26807–26827] with permission from [ACS Publictions], copyright [2024].

3.2.1.4 Protein-modified probiotic therapeutic systems. Mucin is an acid-resistant glycoprotein composed of mucopolysaccharides, commonly found in gastrointestinal mucus.[125] The acid resistance of mucin, combined with its ability to interact with the intestinal mucus layer through hydrogen bonds, disulfide bonds, and hydrophobic interactions, makes it an excellent material for constructing probiotic therapeutic systems.[126] *Akkermansia muciniphila* (AKK) is a probiotic that resides in the mucus layer. Its beneficial activities are primarily exerted through consuming mucin and producing bioactive compounds, which nourish intestinal cells and commensal probiotics.[127,128] Yujie Zhang *et al.* developed an AKK-based therapeutic system, (AKK@GPMGs), which involves modifying AKK successively with proanthocyanidins (PAs), mucin (MUC), and phosphatidylcholine (PC), and then encapsulating it within methacrylate-modified gelatin porous microgels. In this therapeutic system, mucin serves as a sufficient energy source for AKK, promoting its growth and reproduction. Furthermore, AKK@PAs-MUC-PC (AKK@PMP) is released at the inflamed sites in the colon, and the PAs-MUC-PC layer in AKK@PMP

exhibits strong adhesion properties towards the inflamed colon sites, ensuring the colonization of AKK in the intestine.[109] After treatment with AKK@GPMGs, the mucus thickness of colitis mice increased, intestinal permeability decreased, and goblet cell abundance increased, significantly enhancing the beneficial intestinal microbiota while inhibiting harmful microbiota (Fig. 7).

3.2.1.5 Biofilm-modified probiotic therapeutic systems. Biofilms are protective layers produced by bacteria under extreme conditions to counteract external environmental threats, such as displacement caused by physical forces and elimination due to environmental attacks.[129] Biofilms are primarily composed of biomacromolecules, including proteins, polysaccharides, DNA, RNA, peptidoglycan, lipids, and phospholipids.[130] For bacteria, the biofilm not only serves as an adhesive that attaches colonies to surfaces and prevents their removal by flowing liquids but also defends against external threats such as antibiotics and the host immune system by preventing penetration.[131,132] This means that the biofilm can function as part of a therapeutic system, offering both chemical barrier and physical adhesion properties to protect probiotics as they navigate through the complex gastric environment and colonize at sites of colonic inflammation. *Bacillus subtili* (BS) is an important probiotic that can work synergistically with other beneficial gastrointestinal bacteria to support digestion, enzyme production, and the health of the immune and digestive systems.[133] Under appropriate conditions, BS can secrete large amounts of extracellular polysaccharides and proteins such as TasA and BslA, which collectively form a biofilm.[134] Based on this, Xinyue Wang *et al.* used BS as a probiotic model and cultivated it on solid minimal salts glycerol glutamate plates to stimulate the formation of a robust biofilm on the surface of BS. Biofilm-coated BS demonstrated significantly improved gastrointestinal tolerance and adhesion in mice and pigs. Especially in the pig model, the oral bioavailability of biofilm-coated BS was 125 times higher and the colonization rate was 17 times greater compared to uncoated BS.[111]

In summary, probiotic therapeutic systems based on exogenous modification can effectively protect probiotics from the damaging effects of gastric acid, thereby enhancing their survival rate. Different modification materials can impart probiotics with improved adhesion and retention time on the intestinal wall, enabling them to better exert their regulatory effects on the intestinal flora.

3.2.2 Endogenous modified probiotic therapeutic systems. In addition to endowing probiotics with some new characteristics through encapsulation and modification, gene editing technology can also improve the characteristics of probiotics to enhance their stability in complex environments and promote their colonization at intestinal inflammatory sites. The probiotic therapeutic systems constructed based on gene editing technology are referred to as endogenous modified probiotic therapeutic systems. Probiotics possess a vast genome, which provides convenience for their genetic modification. Moreover, from homologous recombination to the first-generation Zinc Finger Nucleases (ZFNs) technology, to the second-generation Transcription Activator-like Effector Nucleases (TALENs) technology, and the more popular third-generation Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated (CRISPR–Cas) technology in recent years, gene editing technologies have provided more powerful tools for editing and modifying microbial genomes.[135] Based on this, genetically engineered probiotics have been designed for the treatment of IBD and we will introduce it in detail through some examples.

Jun Zhou *et al.* genetically engineered ECN to overexpress CAT and SOD (ECN-pE) to alleviate oxidative damage caused by IBD. To improve the bioavailability of ECN-pE, they used chitosan and sodium alginate to coat ECN-pE (ECN-pE$(C/A)_2$). Such engineered EcN-pE$(C/A)_2$ could be effective in relieving inflammation and removing ROS. It also can regulate the gut microbiota and improve the abundance of *Lachnospiraceae_NK4A136* and *Odoribacter*, which could produce an important short-chain fatty acid, butyrate. Butyrate serves not only as a crucial energy source for colonic epithelial cells but also inhibits the release of inflammatory cytokines and upregulates the expression of TJs.[136] eATP is produced by activated immune cells and commensal bacteria and is relevant to IBD.[137] On the one hand, eATP activates purinergic receptors to boost pro-inflammatory cytokine production; on the other hand, eATP activates effector T cells, suppresses regulatory T cell (Treg) responses, and promotes enteric neuron apoptosis.[138–140] Based on the association of eATP with IBD, Benjamin M. Scott *et al.* developed yeast-based engineered probiotics that express a human P2Y2 purinergic receptor which greatly increases the eATP sensitivity. Then they linked the activation of this engineered P2Y2 receptor to the secretion of the ATP-degrading enzyme apyrase thus to create engineered yeast probiotics which can sense a pro-inflammatory molecule and generate a proportional self-regulated response aimed at its neutralization. With the presence of eATP, these yeast-based engineered probiotics responsively secrete the CD39-like eATP-degrading enzyme apyrase. *Clostridium cluster* XIVa is associated with the induction of Treg cells, and it is consistently decreased in patients with IBD. Engineered yeast probiotics show good therapeutic effects on IBD, and the abundance of *Lachnospiraceae*, which is included in the *Clostridium cluster* XIVa, in colitis mice treated with engineered yeast probiotics is significantly higher than that in colitis mice without engineered yeast probiotics treatment.[141] Sulfate-reducing bacteria (SRBs) present in the colon produce hydrogen sulfide (H_2S) from sulfur oxide species extracted from the host and host enzymes detoxify H_2S to thiosulfate.[142,143] Thiosulfate as a biomarker of IBD, is an appealing target for studying the link between gut sulfur metabolism and inflammation.[144] Ting-Ting Fang *et al.* constructed a thiosulfate-responsive engineered bacteria (E-acgEBE-AvG). E-acgEBE-AvG was composed of three units: a timely reporting unit, a single-base-edited unit, a controllable recorded-cell self-lysis, and a drug release unit. In controllable recorded-cell self-lysis and drug release unit, with the presence of thiosulfate and xylose, lysis E was expressed which led to the lysis of the edited bacteria and immunomodulator AvCystain release.[145] Zhen-

Ping Zou *et al.* also developed a kind of ''intelligent'' whole-cell engineered bacteria, i-ROBOT (intelligent responsive bacteria for diagnosis and therapy) which constitutes a self-tunable drug-secreting system that can respond to levels of the inflammatory marker thiosulfate to drive the release of AvCystatin. Mice with colitis treated with i-ROBOT showed reduced levels of inflammatory factors and restored intestinal epithelial tissue.[146] Designing antibodies to reduce the expression of inflammatory cytokines (such as TNF-α) is the most common immunotherapy in IBD.[147] Interferon lambda 1 (IFNL1) as a member of the IL-10 superfamily, signals through various pathways involving IL-10 and type I IFNs, making it a promising candidate to investigate the treatment of IBD.[148] Based on this, Koon Jiew Chua *et al.* engineered probiotic EcN (ECN-IFNL1) to produce and secrete a type III interferon, interferon lambda 1 (IFNL1), in response NO. Then, their experiment demonstrated that IFNL1-expressing EcN strains upregulated Foxp3 expression in T cells and thereafter reduced the production of pro-inflammatory cytokines such as IL-13 and IL-33, significantly ameliorating inflammation. In addition, EcN-IFNL1 can also maintain the intestinal epithelial barrier and restore intestinal homeostasis by promoting the expression of TJs.[149]

In summary, gene editing technology can equip probiotics with new characteristics, such as novel enzymatic activities, new responsiveness, and improved drug-loading capabilities, which not only enhance their stability in complex environments but also significantly broaden their application scope, making them suitable not only for the treatment of IBD but also for its diagnosis.

3.3 Prebiotic-based therapeutic systems

Prebiotics are defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit.[150] Currently, prebiotics mainly include polyphenols,[151] polysaccharides,[152] peptides,[153] microalgae[154] *etc.* They can provide nutrients for beneficial bacteria in the gut, promoting their growth and reproduction, and also enhancing the levels of beneficial metabolites produced by the gut microbiota.[155–157] For example, as a prebiotic, microalgae accumulate substantial fatty acids and other substances beneficial to the growth of intestinal flora, which can be utilized by the intestinal flora to exert a positive regulatory effect on it. However, the efficacy of prebiotics can be limited by their physicochemical properties. For example, the poor oral bioavailability of pure polyphenol prebiotics due to their solubility limits their ability to regulate gut microbiota.[151] The rapid fermentation characteristics of polysaccharides in the intestine may lead to a shortage of fermentable carbohydrates for bacteria in the distal colon, affecting the stability of gut microbiota.[158] Therefore, it is necessary to take measures to address the challenges faced by prebiotics in the process of exerting their efficacy. Researchers have done a lot of work to address these challenges by constructing therapeutic systems to deliver prebiotics, which is an effective strategy to improve their bioavailability and prolong their action time at the site of colonic inflammation. In addition, the characteristics of prebiotics, such as their resistance to gastric acid and non-hydrolysis by relevant enzymes in the gastrointestinal tract, also make them suitable as carriers for drug delivery.[159] For instance, the bioactive microalgae Spirulina platensis (SP) possesses excellent biocompatibility, cost-effectiveness, a large active surface area, remarkable stability, and resistance to gastric acid, making it an ideal natural carrier for drug delivery[160] Based on this, we classify prebiotic therapeutic systems into two categories: those aimed at delivering prebiotics and those that utilize prebiotics as carriers, and we will provide detailed introductions to both in this part.

3.3.1 Therapeutic systems for prebiotic delivery. The hydrophobicity of polyphenol prebiotics is the main reason for their poor bioavailability. The therapeutic systems based on PLGA have particular advantages in delivering hydrophobic drugs, as they can further improve the solubility of these drugs and exhibit high encapsulation efficiency.[161] Xiangji Yan *et al.* have developed a P-selectin binding peptide-decorated poly lactic-*co*-glycolic acid nanoparticle (PBP-PLGA-NP) as a carrier to load hydrophobic polyphenol prebiotic resveratrol. The PBP-PLGA-NP delivery platform significantly enhances the bioavailability of resveratrol, and through colon targeting, ensures its precise release at the site of inflammation, effectively alleviating intestinal inflammation and improving gut microbiota.[162] Polysaccharide prebiotics exert their therapeutic effects primarily through fermentation by gut microbiota, therefore, the efficacy of polysaccharide prebiotics is closely related to their retention time in the intestine. Yeast β-glucan isolated from *Saccharomyces cerevisiae* is a typical polysaccharide prebiotic fermented by gut microbiota, which can selectively promote the growth of probiotics.[163,164] Fan Yang *et al.* encapsulated derivatives of β-glucan within a polydopamine coating (PDA) through self-assembly. PDA, rich in catechol groups, can effectively adhere to the colonic epithelium, thereby prolonging the retention time of β-glucan at the site of colonic inflammation in the intestine and enhancing the prebiotic activity to improve the gut microbiota.[165] In addition, gel exhibits excellent colonic adhesion due to its unique physical and chemical properties, and is capable of effectively prolonging the retention time of drugs. Inulin, a typical polysaccharide prebiotic fermented by gut microbiota, can increase the diversity and abundance of commensal bacteria.[166] Zhuangzhuang Zhang *et al.* developed an inulin gel and used it to form a macroporous composite material with nanoneedles to improve inflammation and regulate intestinal flora. After oral administration, the macroporous composite material exhibited good intestinal adhesion, greatly increasing the retention time of inulin in the intestine (Fig. 8).[167]

3.3.2 Therapeutic systems composed of prebiotic. Some prebiotics possess inherent abilities such as flexible structure, good biocompatibility, controlled release behavior, adjustable degradation kinetics, and protective capabilities, making them excellent carriers for drug delivery.[168] Inulin can not only be used as an active substance for delivery but also serves as an excellent carrier due to its chemical modifiability and gastric acid resistance. Qijuan Sun *et al.* grafted 4-aminothiophenol (ATP) onto carboxymethyl inulin (CMI) to create a nanocarrier for loading budesonide. The ATP modification transformed the inulin into an amphiphilic polymer, effectively addressing the

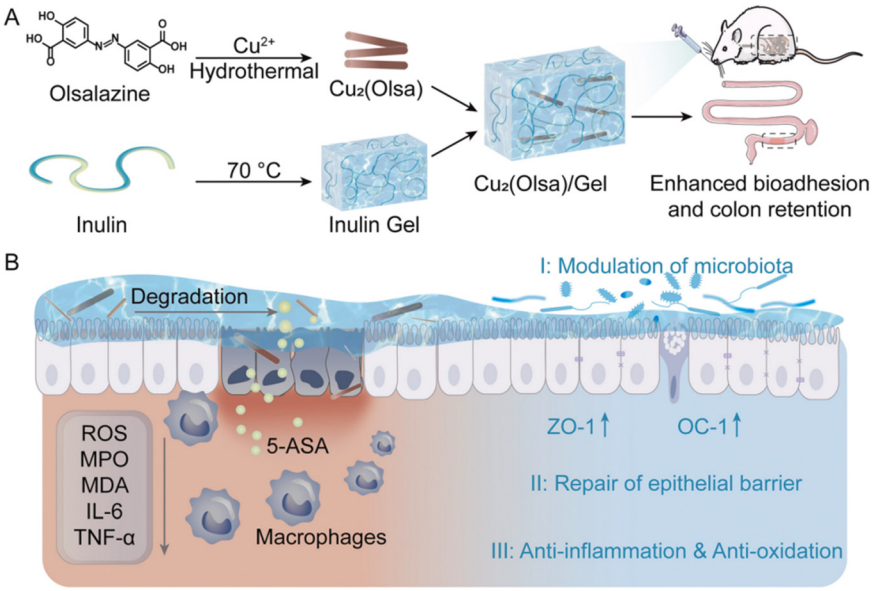

Fig. 8 Schematic illustration of Cu_2(Olsa) and inulin gel composite for IBD treatment by restoring intestinal homeostasis. (A) Preparation of Cu_2(Olsa)/Gel. (B) The proposed therapeutic mechanisms of Cu_2(Olsa)/Gel. Reprinted from Z. Zhang, Y. Pan and Z. Guo *et al.*, An olsalazine nanoneedle-embedded inulin hydrogel reshapes intestinal homeostasis in inflammatory bowel disease, *Bioact. Mater.*, **33**, 71–84, Copyright (2024), with permission from Elsevier.

poor water solubility of budesonide and significantly enhancing its bioavailability (Fig. 9).[169] Microalgae are photosynthetic microorganisms rich in protein, polysaccharides, minerals, and various vitamins, which can exert a positive influence on the gut microbiota.[170,171] The special structures of some microalgae can ensure that drugs pass through the complex gastrointestinal environment, protecting the drugs from successfully reaching the colon and exerting their therapeutic effects. Danni Zhong *et al.* constructed a therapeutic system based on bioactive microalgae SP for loading curcumin to treat ulcerative colitis. The gastric acid resistance and stability of SP ensure the smooth delivery of curcumin to the site of colonic inflammation. Subsequently, SP is captured by intestinal villi, gradually degraded, and releases curcumin, thereby achieving an ideal

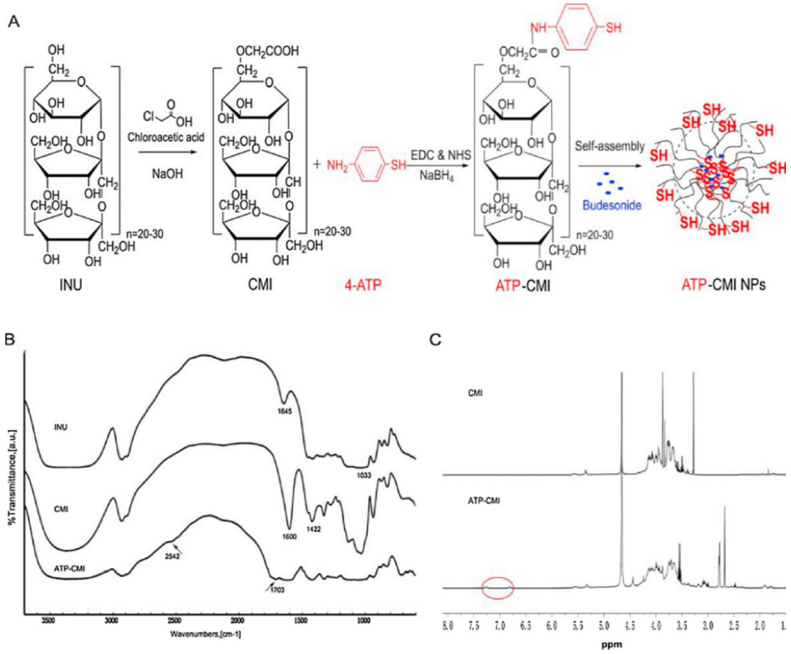

Fig. 9 (A) Synthetic procedure of CMI, ATP-CMI conjugate and ATP-CMI NPs. (B) FT-IR spectrums of INU, CMI, and ATP-CMI conjugate. (C) ^{1}H NMR spectra of CMI and ATP-CMI conjugate in D_2O. Reprinted from Q. Sun, L. Luan and M. Arif *et al.*, Redox-sensitive nanoparticles based on 4-aminothiophenol-carboxymethyl inulin conjugate for budesonide delivery in inflammatory bowel diseases, *Carbohydr. Polym.*, **189**, 352–359, Copyright (2018), with permission from Elsevier.

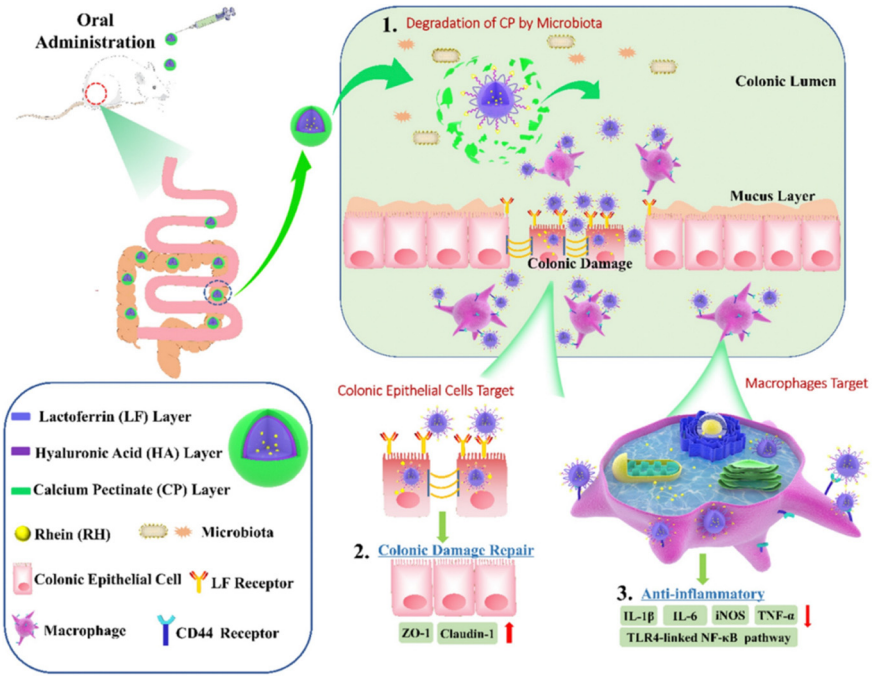

Fig. 10 Schematic illustration of using CP/HA/RH-NPs in the treatment of UC in mice. (1) Schematic illustration of the passage of orally administered CP/HA/RH-NPs through GIT. CP could protect CP/HA/RH-NPs from passing through the stomach and small intestine, and further release HA/RH-NPs into the colonic lumen due to its degradation. (2) Schematic illustration of enhancing the effects of RH in repairing intestinal damage by adjusting ZO-1 and Claudin-1 expression in the UC mice model by colonic epithelial cell target. (3) Schematic illustration of targeting macrophage could effectively promote RH's anti-inflammatory effect through the TLR4/MyD88/NF-κB pathway in *in vivo* anti-UC therapeutic efficacy. Reprinted from R. Luo, M. Lin and C. Fu *et al.*, Calcium pectinate and hyaluronic acid modified lactoferrin nanoparticles loaded rhein with dual-targeting for ulcerative colitis treatment, *Carbohydr. Polym.*, **263**, 117998, Copyright (2021), with permission from Elsevier.

drug distribution in the intestine without causing adverse reactions.[172] Pectin is a natural and food-grade polysaccharide prebiotic obtained from the primary cell wall of plants, which can overcome the instability of the treatment system in the stomach.[173] Rhein (RH) has good anti-inflammatory effects, but its oral bioavailability is poor due to its limited solubility.[174] Ruifeng Luo *et al.* have developed a nanocarrier formed by modifying lactoferrin with calcium pectinate (CP) and hyaluronic acid (HA), which is used to load RH to improve its bioavailability. CP layer makes CP/HA/RH-NPs more stable and protects RH from destruction in the gastrointestinal environment (Fig. 10).[175] In addition, some prebiotics can also be used to achieve controlled drug release due to their good responsiveness to the intestinal microenvironment. Alginate is an anionic polysaccharide with good biocompatibility and biodegradability. Due to its ionizable carboxylic acid groups, it can undergo reversible protonation and deprotonation in different pH environments to achieve responsive drug release.[176] Xue Di Zhang and his colleagues modified alginate with polypropylene sulfide to load AST (AST@RS-PPS). After 180 minutes of UV irradiation, the retention rate of AXT in AST@RS-PPS was 58.46 ± 0.25%, which was 5.24 times higher than that of free AXT. After a 6-hour treatment in a 60 °C water bath, the retention rate of AXT in AST@RS-PPS was 78.94 ± 1.44%, representing 4.6 times that of free AXT. This modified RS-PPS protects the structural stability of AST. In addition, the results of animal experiments indicate that AST@RS-PPS can significantly alleviate colitis, protect the integrity of colonic tissue, restore the expression of tight junction proteins ZO-1 and occludin, and increase the abundance of beneficial bacteria. Compared to the control group and DSS group, the RS@PPS group significantly upregulated the abundance of *Lachnospiraceae*_NKA136 and *Clostridia*. The increase in the abundance of *Lachnospiraceae*_NKA136 and *Lachnospiraceae* is beneficial for the alleviation of colitis and the production of short-chain fatty acids (Fig. 11).[177]

In summary, by constructing therapeutic systems that deliver prebiotics to sites of intestinal inflammation, their retention time in the intestine can be extended, maximizing their ability to modulate the intestinal microbiota. Additionally, utilizing prebiotics as encapsulating materials to deliver other drug molecules can effectively enhance the bioavailability of these drug molecules, significantly improving their therapeutic efficacy.

3.4 Gut microbiota metabolites-based therapeutic systems

The gut microbiota metabolites are one of the primary modes of interaction between the gut microbiota and the host.[178] The gut microbiota metabolites mainly include SCFAs, tryptophan derivatives, and secondary bile acids.[179] In a healthy state, gut microbiota metabolites contribute to maintaining the host's basic functions, including facilitating the absorption of nutrients, promoting the growth and development of IECs, and maintaining immune homeostasis.[180] However, in an

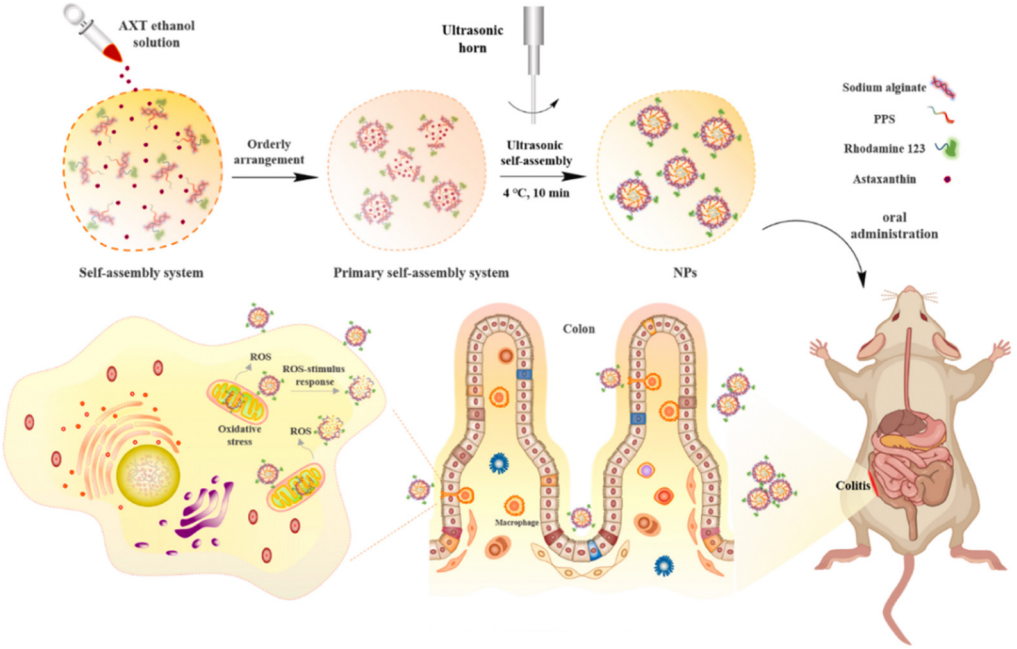

Fig. 11 Preparation of ROS/pH dual-responsive AXT-loaded nanoparticles and their application in the treatment of colitis. Reprinted from X. Zhang, X. Zhao and Z. Hua *et al.*, ROS-triggered self-disintegrating and pH-responsive astaxanthin nanoparticles for regulating the intestinal barrier and colitis, *Biomaterials*, **292**, 121937, Copyright (2023), with permission from Elsevier.

inflammatory state, the metabolism of gut microbiota becomes disrupted, causing a decrease in the levels of these "beneficial" metabolic products, which further exacerbates the inflammation by losing the positive regulatory effects on the intestinal microenvironment.[181] With the gradual deepening of research into gut microbiota and its metabolites, researchers have found that directly supplementing gut microbiota metabolites can effectively reverse the disrupted state of the gut microbiota, restore the positive regulatory effects of gut microbiota metabolites on the intestinal microenvironment, and inhibit the further spread of intestinal inflammation. For example, supplementing with SCFAs can regulate the recognition of the innate immune system, thereby inhibiting the progression of intestinal inflammation.[182] However, therapies based on gut microbiota metabolites are often limited by bioavailability, preventing them from maximizing their therapeutic efficacy. An effective means to enhance the therapeutic efficacy is to construct a therapeutic system that carries gut microbiota metabolites for precise release at the site of the lesion. In this section, we will separately introduce SCFAs, tryptophan derivatives, and secondary bile acids, along with the therapeutic effects of therapeutic systems based on these gut microbiota metabolites for IBD.

3.4.1 Short-chain fatty acids. SCFAs are carboxylic acids containing 1–6 carbon atoms, primarily produced by the anaerobic fermentation of dietary fiber.[183] They provide energy for epithelial cells to maintain the epithelial barrier and participate in maintaining intestinal immune homeostasis.[132] Butyrate, as a representative of SCFAs, has been clearly shown to regulate the gut microbiota by increasing the abundance of beneficial bacteria in DSS-induced colitis mice.[184] However, butyrate can be rapidly metabolized in the body, resulting in a short half-life, which limits its ability to fully exert its therapeutic effects.[28] XXi Fan *et al.* employed poly(ethylene glycol)-*block*-polymethylmethacrylate as the backbone and covalently attached butyrate to this backbone through disulfide bonds, subsequently forming the polymer nanoparticle (PSBA). With a butyrate content as high as 22%, PSBA achieved the responsive release of butyrate at the site of colonic inflammation, significantly enhancing its bioavailability (Fig. 12).[185]

3.4.2 Tryptophan derivatives. Tryptophan can be metabolized by the gut microbiota into indole derivatives (such as indole-3 acetic acid, indole-3 propionic acid, *etc.*),[186] which can play an immunomodulatory role by activating AHR receptors, thereby alleviating inflammation and regulating gut microbiota.[187] Indole-3 propionic acid (IPA), a tryptophan derivative with anti-inflammatory properties, can reduce the expression of pro-inflammatory factors in colitis mice and increase the abundance of beneficial bacteria to treat IBD.[188] However, the poor oral administration efficiency limits its therapeutic effectiveness. Keli Yang *et al.* ensured the successful encapsulation of IPA in prebiotic microcapsules composed of alginate and resistant starch (RS) through an electrostatically driven microfluidics platform (IPA@MC), significantly enhancing the bioavailability of IPA. Additionally, IPA@MC demonstrated excellent capability in modulating gut microbiota (Fig. 13).[189] Indole-3-acetic acid (IAA), as an important AHR receptor agonist among tryptophan derivatives, can regulate the gut microbiota under inflammatory conditions by modulating immune homeostasis.[190] However, since indole-3-acetic acid (IAA) is absorbed in the upper digestive tract, especially in the small intestine, the direct oral administration of IAA results in

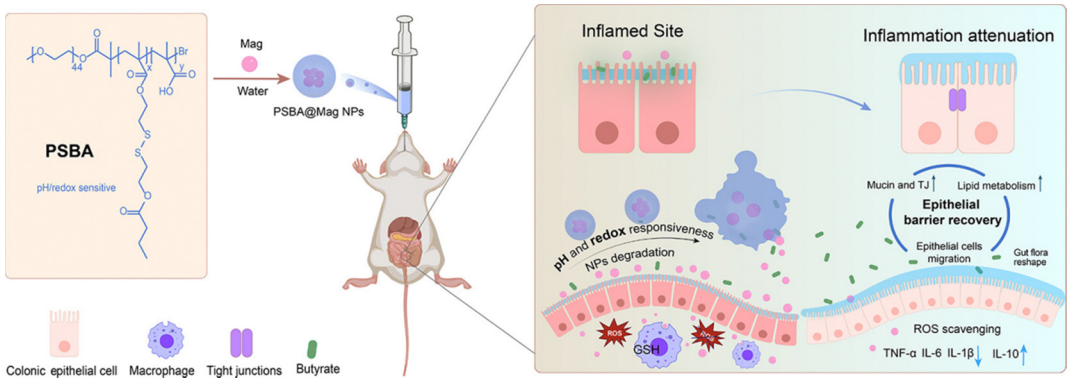

Fig. 12 Magnolol-incorporated pH and redox dual responsive butyrate-based polymeric nanoparticles (PSBA@Mag) as an oral nanomedicine to treat inflammatory bowel disease by improving epithelial barrier repair and inflammation mitigation. Reproduced from reference [X. Fan, Z. Z. Zhang and W. X. Gao *et al.*, An Engineered Butyrate-Derived Polymer Nanoplatform as a Mucosa-Healing Enhancer Potentiates the Therapeutic Effect of Magnolol in Inflammatory Bowel Disease, *ACS Nano*, 2023, **18**(1), 229–244] with permission from [ACS Publications], copyright [2023].

low bioavailability. To effectively deliver IAA to the site of colonic inflammation, Yingying Song *et al.* synthesized HAMSIAA by connecting IAA to high amylose maize starch (HAMS) through esterification. HAMSIAA can protect IAA from the stimulated gastric acid environment to reach the inflammatory site, where HAMS is metabolized by intestinal flora into short-chain fatty acids, while IAA alleviates intestinal inflammation by activating AHR receptors.[191]

3.4.3 Secondary bile acids. Bile acids (BAs) include primary bile acids (PBAs) and secondary bile acids (SBAs). PBAs, synthesized from cholesterol in the liver, are modified by gut microbiota into SBAs.[192] SBAs primarily include lithocholic acid (LCA), deoxycholic acid (DCA), and ursodeoxycholic acid (UDCA), among others. They can function as signaling molecules, interacting with membrane receptors such as Takeda G protein-coupled receptor 5 (TGR5), nuclear receptors, and their downstream metabolic enzyme transporters to influence the dynamics of the microbiome and regulate various inflammatory pathways.[193] Studies have shown that the levels of SBAs are closely related to the development of IBD. Yang *et al.* found that the levels of certain SBAs in the feces of UC patients were significantly lower than those in healthy individuals.[194] The decrease in SBAs levels can affect the expression of TJs and the renewal of intestinal stem cells, leading to damage to the intestinal barrier and subsequently exacerbating IBD.[195] Therefore, the treatment of IBD may be achieved. By supplementing SBAs to activate the relevant key signaling pathways. For instance, LCA can enhance anti-inflammatory effects by modulating the TGR5-cAMP-PKA

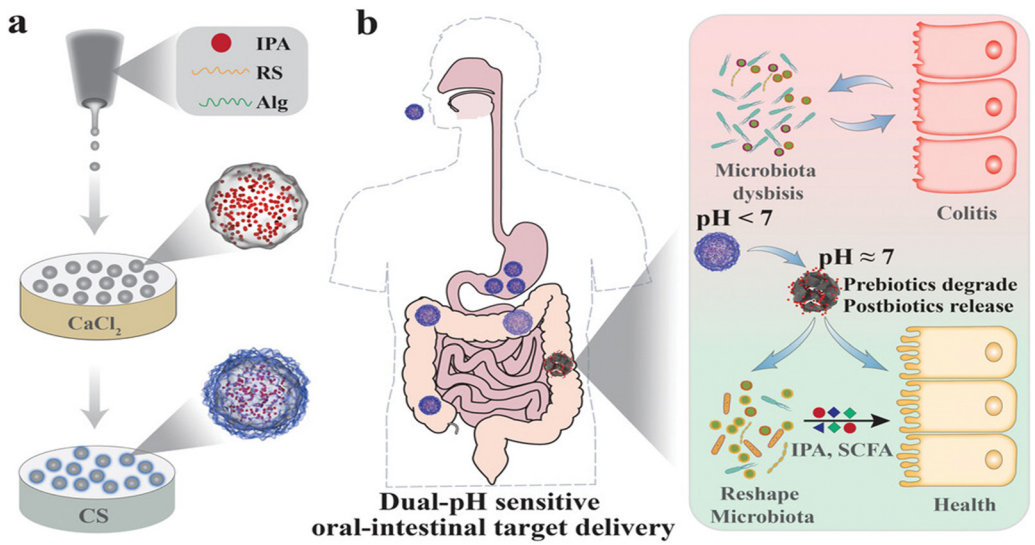

Fig. 13 Schematic illustration of the prebiotics encapsulating postbiotic microcapsules (IPA@MC) for preventing and treating colitis. (a) The microfluidic electrospray procedures for generating IPA encapsulating Alg/RS microcapsules further coated by chitosan. (b) The dual-pH sensitive core–shell structure allows a slow drug release in the acid condition of the upper gastrointestinal tract and a rapid drug release in the neutral condition of the lower gastrointestinal tract to exert the protective effects against colitis *via* modulating gut microbiota. Alg: alginate; RS: resistant starch; CS: chitosan; IPA: indole-3-propionic acid. Reproduced from reference [K. Yang, X. Wang, R. Huang, H. Wang, P. Lan and Y. Zhao, Prebiotics and Postbiotics Synergistic Delivery Microcapsules from Microfluidics for Treating Colitis, *Adv. Sci.*, 2022, **9**(16)] with permission from [Wiley], copyright [2022].

pathway, thereby preventing the activation of the NLRP3 inflammasome. Stimulation of TGR5 with LCA can trigger PKA kinase activity, leading to the activation of the TGR5-cAMP-PKA pathway, which subsequently results in the phosphorylation and ubiquitination of NLRP3.[196] However, to date, the therapeutic systems based on SBAs still require development and refinement. This may be because the mechanisms of action of BAs in clinical studies are still under exploration. Several studies have demonstrated the therapeutic effect of SBAs in the treatment of IBD. This therapeutic effect relies on the activation of relevant signaling pathways and the expression of bile acid receptors, such as FXR, GPBAR1, PXR, VDR, and RORγt.[197] However, agonists targeting specific bile acid receptors have yet to be developed, and the therapeutic potential of SBAs-based therapies remains understudied. The mechanism of action of SBAs in clinical studies is still being explored, which points the way forward for our future research and the development of therapeutic systems.

In summary, by constructing therapeutic systems to deliver metabolites of gut microbiota, can effectively enhance their bioavailability and better leverage the regulatory effects of gut microbiota.

3.5 Extracellular vesicles-based therapeutic systems

Extracellular vesicles (EVs) are nanometer-sized lipid bilayer-delimited particles secreted by almost all types of cells, including bacteria, mammals, and plants, and are considered to be mediators of intercellular communication.[198] Based on their sources, EVs can be classified into bacterial extracellular vesicles (BEVs), animal extracellular vesicles (AEVs), and plant extracellular vesicles (PEVs). The size, composition, and cargo of EVs from different sources vary, enabling them to play unique roles in various biological processes that regulate the function and composition of the gut microbiota. PEVs are capable of carrying natural product molecules with excellent bioactivity, which exert immunoregulatory effects, facilitate tissue repair, and improve the growth environment of the gut microbiota.[199] AEVs can target specific signaling pathways to reduce inflammation, strengthen tight junctions, and inhibit NF-κB-mediated apoptosis.[200] BEVs undertake the task of signal communication between bacteria and among bacteria, as well as between bacteria and their hosts. Consequently, they can carry relevant functional molecules to directly impact the gut microbiota and influence its abundance.[201] These three types of EVs can themselves serve as a therapeutic system, exerting significant effects on maintaining homeostasis, regulating immune responses, as well as the composition and function of the gut microbiota. Additionally, their excellent biocompatibility and low immunogenicity make them ideal biomaterials for drug delivery. In this section, we will provide a detailed introduction to these three types of EVs and their therapeutic systems.

3.5.1 Bacterial extracellular vesicles. Bacterial extracellular vesicles (BEVs) are spherical nanostructures composed of a lipid bilayer secreted by bacteria, with a size range of 20 to 300 nm. By delivering these encapsulated bioactive molecules, BEVs interact with other microorganisms, host cells, and the host immune system, thereby influencing the microbial ecosystem and participating in the preservation of intestinal barrier function.[198] In a healthy state, the secretion of BEVs is a natural phenomenon that plays a role in maintaining intestinal homeostasis. However, when IBD occurs, the BEVs secreted by the microbiota are disrupted, failing to provide normal protection to the intestine, thereby allowing the development of intestinal dysbiosis and its potential pathogenic consequences. Therefore, supplementing BEVs secreted by probiotics can effectively regulate the intestinal microbiota and treat IBD. The regulatory role of BEVs on the gut microbiota is primarily achieved through two mechanisms, the first of which is stimulating the restoration of the host's IEB. The EVs produced by *Escherichia coli* Nissle 1917 are capable of attaching to receptors on the surface of IECs, triggering the nucleotide-binding oligomerization domain 1 (NOD1) signaling pathway to enhance the expression of TJs, thereby restoring the IEB.[202] Another mechanism is to foster symbiotic growth or, conversely, restrict the proliferation of pathogenic microorganisms through direct interaction with other bacteria. For instance, direct oral administration of EVs from *Akkermansia muciniphila* can directly promote the growth of probiotics and inhibit the proliferation of pathogenic bacteria. Hwa Seung Han *et al.* employed a tangential flow filtration system to isolate *Roseburia intestinalis*-derived EVs with a diameter of 76 nm from *Roseburia intestinalis*. They demonstrated that orally administered *Roseburia intestinalis*-derived EVs could effectively accumulate in inflamed colonic tissue and increase the abundance of *Bifidobacteria* (Fig. 14).[203]

3.5.2 Plant extracellular vesicles. Plant extracellular vesicles (PEVs) are spherical lipid nanostructures secreted by plants, with a size range of 30 to 500 nm. As natural nanoparticles containing lipids, proteins, nucleic acids, and secondary metabolites, PEVs can exert anti-inflammatory activity and regulate gut microbiota by transporting these functional substances to receptor cells to mediate intercellular communication. A study has demonstrated that EVs derived from ginger can treat colitis by inhibiting the spread of inflammation, reducing the expression of proinflammatory cytokines, as well as increasing the levels of anti-inflammatory cytokines such as IL-10 and IL-22, thereby promoting the restoration of the IEB.[204] EVs derived from grapefruit can be ingested by intestinal macrophages and inhibit the production of IL-1β and TNF-α in these macrophages by upregulating the expression of heme oxygenase-1 (HO-1), thereby improving dextran sulfate sodium (DSS)-induced colitis in mice. PEVs derived from tea have been shown to directly exert a positive influence on the diversity of the gut microbiota. These tea-derived PEVs have been identified to increase the ratio of *Bacteroidetes*/*Firmicutes* and enhance the overall abundance of fecal bacteria.[205] In addition, PEVs have tremendous potential to serve as sustainable, green, and efficient nanocarriers for drug delivery.[199] However, their application is still hindered by shortcomings such as low targeting efficiency and poor homogeneity. By integrating PEVs into a holistic therapeutic system, functionalizing them through

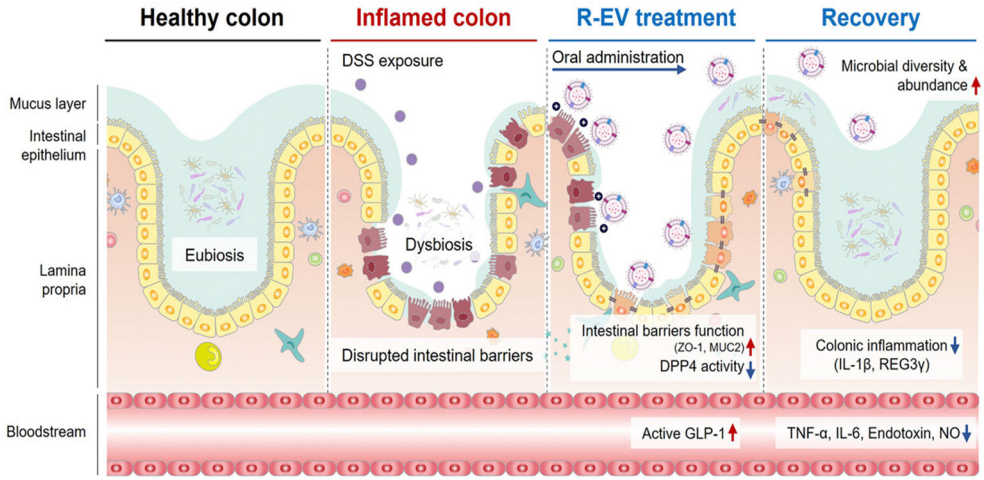

Fig. 14 Schematic illustration of Roseburia-derived extracellular vesicles (R-EVs) as a critical mediator for DSS-induced IBD treatment. R-EVs exert amicable alterations in dysbiosis, reduce the inflammatory response, and restore the intestinal barrier in IBD. Reproduced from reference [H. S. Han, S. Hwang and S. Y. Choi *et al.*, *Roseburia intestinalis*-derived extracellular vesicles ameliorate colitis by modulating intestinal barrier, microbiome, and inflammatory responses, *J. Extracell. Vesicles*, 2024, **13**(8)] with permission from [Wiley], copyright [2024].

surface modification and cargo loading, and enhancing their binding to specific target cells, their range of applications can be significantly expanded. For example, modifying PEVs through the insertion of polyethylene glycol (PEG)-lipids can prolong their circulation time in the blood, improve their stability, and effectively deliver them to the site of disease through enhanced permeability and retention (EPR) effects.[206] Curcumin, which possesses potent anti-inflammatory activity, was encapsulated into tomato-derived EVs through direct incubation, ultrasonic treatment, and extrusion. In this therapeutic system, the tomato-derived EVs served as carriers for the transport of curcumin, significantly enhancing its anti-inflammatory activity.[207]

3.5.3 Animal extracellular vesicles. Animal extracellular vesicles (AEVs) are spherical lipid nanostructures secreted by animals, with a size range of 30 to 1500 nm. The sources of AEVs include animal milk, IECs, immune cells, various bone marrow mesenchymal stem cells (MSCs), and others.[208] AEVs from different cellular sources can exert positive regulatory effects on intestinal microbiota in various ways. EVs derived from raw milk can directly impact the gut microbiota by

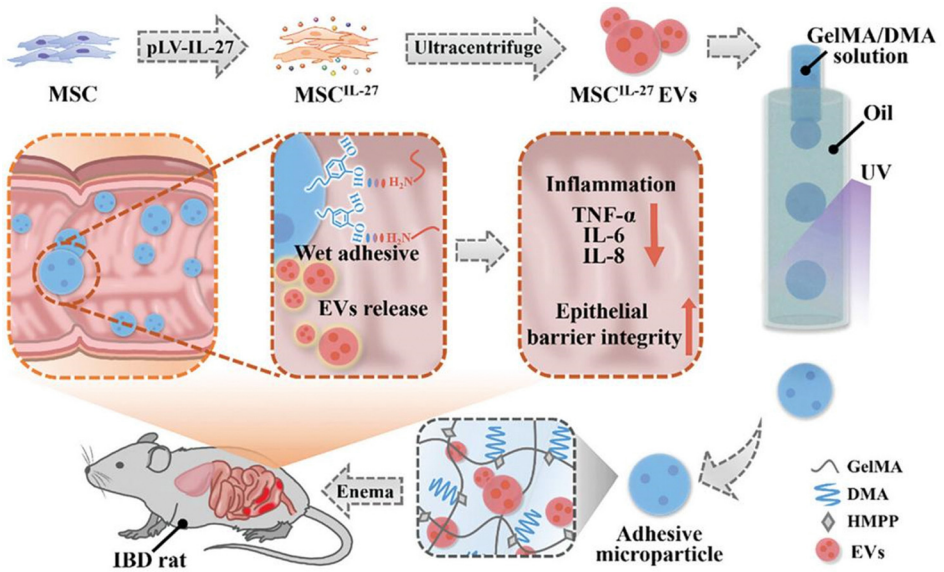

Fig. 15 Schematics of the fabrication and application of the wet-adhesive microparticles with MSCIL-27 EVs loaded for IBD treatment. The MSCIL-27 EVs prepared *via* lentivirus-mediated gene transfection technology and ultracentrifuge were encapsulated into DMA-modified GelMA through a microfluidic method. Reproduced from reference [M. Nie, D. Huang, G. Chen, Y. Zhao and L. Sun, Bioadhesive Microcarriers Encapsulated with IL-27 High Expressive MSC Extracellular Vesicles for Inflammatory Bowel Disease Treatment, *Adv. Sci.*, 2023, **10**(32)] with permission from [Wiley], copyright [2023].

increasing the abundance of ''beneficial'' microorganisms such as *Akkermansia*, *Muribaculum*, and *Turicibacter*, while simultaneously decreasing the levels of the ''harmful'' bacterium *Desulfovibrio*.[209] EVs produced by IECs exhibit TGF-β1-dependent immunosuppressive activity, and they induce regulatory T cells and immunosuppressive dendritic cells in an epithelial cell adhesion molecule-dependent manner to treat IBD.[210] EVs derived from MSCs can inhibit the M1 polarization of macrophages and reduce the levels of inflammatory cytokines, thereby remodeling the intestinal microenvironment.[211] Furthermore, as a therapeutic system, the phospholipid membrane structure of AEVs provides support for subsequent targeted modifications. By anchoring galactose to the surface of extracellular vesicles (EVs) loaded with IL-10 and secreted from genetically engineered mammalian cells (Gal-IL10-EVs), Jingang Liu *et al.* have endowed the EVs with the ability to target galactose-type lectins of macrophages on the surface of macrophages. The further modification of Gal-IL10-EVs with chitosan/alginate (C/A) granted them the ability to endure harsh gastric environments.[212] Min Nie *et al.* have developed EVs derived from MSCs that carry IL-27 ($MSC^{IL\text{-}27}$ EVs). Subsequently, they encapsulated the $MSC^{IL\text{-}27}$ EVs into dopamine methacrylamide-modified hydrogels, enabling the $MSC^{IL\text{-}27}$ EVs to achieve the desired sustained-release effect and effective wet adhesion properties. The therapeutic system based on $MSC^{IL\text{-}27}$ EVs can firmly anchor onto the colonic surface, reduce inflammatory responses, and repair damaged barriers to treat IBD (Fig. 15).[213]

In summary, EVs from different biological sources, as a therapeutic system, can regulate intestinal microbiota through various means. Surface modification of EVs enables them to overcome the gastric acid environment and achieve better targeting, thereby enhancing their therapeutic efficacy in treating IBD.

4 Other therapies related to NGMMs

In the preceding text, we summarized the impact of therapeutic systems based on NGMMs on the gut microbiota. Fecal microbiota transplantation (FMT) and synbiotics are traditional therapies that utilize microorganisms or active substances of natural origin with the ability to regulate intestinal microbiota for the treatment of IBD. Therefore, they are closely related to NGMMs. In this section, FMT and synbiotics are classified as therapies related to NGMMs, and introductions to them are provided.

4.1 Fecal microbiota transplantation

FMT is a therapy that involves collecting feces or fecal matter from a healthy donor and introducing it into the gastrointestinal tract of a patient to correct the ecological imbalance and restore health.[214] The gut microbiota composition of IBD patients undergoes profound alterations, resulting in a severe disruption of the intestinal ecology. Consequently, FMT, which exerts its therapeutic effect by altering the gut microbiota composition, emerges as a promising treatment for IBD.[215] Vaughn *et al.* investigated the therapeutic effect of FMT on CD and found that FMT increased the gut microbiota diversity in CD patients after treatment. In this study, clinical responses improved in 11 out of 19 patients (58%).[216] Kunde *et al.* administered FMT *via* enema once daily for five consecutive days to nine patients with UC. Among these patients, seven experienced symptomatic relief just one week after the treatment.[217] However, many studies have also reported severe side effects associated with FMT therapy in the treatment of IBD. Common side effects following FMT include fever and gastrointestinal symptoms (abdominal discomfort, flatulence, diarrhea, constipation, and vomiting).[218] The potential reason for such outcomes may be that exposure to the new microbiota can provoke a disproportionate immune response in the host towards the transplanted microbiota. The immune response of the host to FMT may lead to an exacerbation of IBD disease activity and further side effects.[219] Furthermore, the clinical administration of FMT *via* enema significantly reduces patient compliance, which to some extent limits its application. To address these issues, Shuang Zhen *et al.* constructed alginate microspheres for the encapsulation of fecal microbiota. They found that this therapeutic system exhibited controlled release capabilities, capable of protecting the fecal microbiota from the effects of gastric acid and digestive enzymes, thereby effectively treating IBD.[220]

4.2 Synbiotics

Synbiotics is a therapy that combines probiotics and prebiotics, exerting synergistic beneficial effects on the host's health.[53] Specifically, this synergistic effect refers to the fact that probiotics can directly regulate the balance of the intestinal ecology and increase the abundance of beneficial bacteria, while prebiotics provide energy for the growth and reproduction of probiotics, thereby enhancing their activity.[221] Using synbiotics to regulate gut microbiota for the treatment of IBD has emerged as a promising approach. Based on the mechanism by which synbiotics exert their effects, Kolida and Gibson have categorized synbiotics into two types: complementary synbiotics and synergistic synbiotics.[222] Among the synbiotics commonly used for the treatment of colitis, the most prevalent is the complementary synbiotic, which is defined as a mixture of probiotics and prebiotics that are selected to function individually to improve IBD. For instance, Steed *et al.* found that a mixture of inulin and *Bifidobacterium longum* (FOS) can effectively improve the abundance of gut microbiota in patients with CD.[223] In this case, inulin and Bifidobacterium serve as a complementary synbiotic. However, a limitation of this therapy is that the prebiotic does not selectively promote the growth of the supplemented probiotic. Instead, the presence of the prebiotic increases the overall abundance of gut microbiota rather than specifically targeting the supplemented probiotic. Therefore, there is a need for a method to enhance the efficacy of multiple probiotics and prebiotic species in combination with complementary synbiotics. Synergistic synbiotics provide a direction for overcoming the limitations of synbiotic therapy.

Synergistic synbiotics refer to the supplementation of prebiotics that selectively stimulate the growth and reproduction of the supplemented probiotics, thereby facilitating the colonization of the supplemented probiotics in the intestine.[224] For instance, Yujie Zhang has developed a therapeutic system utilizing multifunctional inulin/*trans*-ferulic acid/silk protein nanoparticles to load *Bifidobacterium*. In this therapeutic system, inulin serves as a prebiotic, promoting the rapid proliferation of Bifidobacterium and enabling it to exert its effects within a short period of time.[225] In this therapeutic system, inulin and *Bifidobacterium* function in a synergistic way. The presence of inulin selectively promotes the colonization of *Bifidobacterium* in the intestine, enabling it to exert its effects more effectively.

In summary, FMT and synbiotics have shown great potential in treating IBD by regulating the gut microbiota. However, the toxic and side effects of FMT and the low synergism of complementary synbiotics have limited their further application. Nevertheless, therapeutic systems based on these two therapies can effectively address their limitations in the application process, helping them to maximize their therapeutic efficacy.

5 Conclusions and prospects

NGMMs, due to their widespread sources, ease of access, and excellent ability to regulate gut microbiota, have made significant progress in the treatment of IBD. However, their application is hindered by their inherent chemical properties or the complex environment of the gut. By constructing therapeutic systems based on NGMMs, it is possible to overcome the limitations of solubility, half-life, the harsh gastric environment, and the complex inflammatory gut environment, thereby enhancing their ability to regulate gut microbiota. However, this does not mean that they are perfect, nor can they permanently resolve all the issues encountered in the treatment of IBD through modulation of the gut microbiota. Next, we will separately introduce the current issues and suggest the focus of future work for each of them.

(1) Safety: the majority of validations concerning the regulatory effects of phytonutrients on gut microbiota rely heavily on animal models, and their safety has yet to be clinically verified. Although probiotics are currently used in clinical treatment, there have been reports of potential side effects such as infections and allergic reactions. For instance, *Akkermansia muciniphila* benefits the host by degrading mucin in the mucus layer, but the degradation of mucin may exacerbate IBD. Alterations in specific genes of genetically engineered probiotics may accumulate during their growth and reproduction, potentially evolving into superbugs. Large doses of prebiotics exert an osmotic effect in the intestinal lumen and undergo fermentation in the colon, which may cause gaseousness and bloating. Although gut microbiota metabolites can effectively regulate the gut microbiota, they may also have adverse effects on the human body, and determining the appropriate dosage of these metabolites poses a difficult challenge.

(2) Molecular mechanisms: the interaction between phytonutrients and gut microbiota still requires further research, particularly in areas such as how phytonutrients exert their regulatory effects on gut microbiota, how gut microbiota metabolize phytonutrients, and what effects their metabolites have on the host. Additionally, although articles have reported the positive regulatory role of SBAs in IBD, the molecular mechanisms underlying their function still require further exploration to unlock their therapeutic potential and lay the foundation for the development of SBA-based therapeutic systems.

(3) Preparation process: for NGMMs in compound form, including phytonutrients, prebiotics, and gut microbiota metabolites, their solubility in water is poor. Therefore, during the encapsulation process of constructing therapeutic systems, they need to be dissolved in organic solvents. However, completely removing these organic solvents during subsequent preparation steps often poses a challenge. Residual organic solvents may potentially impact the therapeutic process and even cause toxic or adverse effects on patients. For probiotic-based therapeutic systems, the current main encapsulation methods include extrusion and self-assembly. The extrusion process can affect the vitality of probiotics, while the self-assembly, generally conducted under relatively mild conditions, will not affect the vitality of probiotics. However, this encapsulation method relies on electrostatic interactions and may face the risk of leakage in the complex digestive tract environment after oral administration.

(4) Individual variability: different IBD patients have varying compositions of gut microbiota and varying severities of the disease. As a result, they may have different reactions to the same probiotics and prebiotics. Even for the same patient, their reactions may vary at different stages of IBD.

To fully leverage the immense potential of NGMMs and their therapeutic systems in treating IBD, it is imperative to conduct in-depth exploration and practical application targeting the aforementioned issues of safety, individual differences, drug dependence, manufacturing processes, and encapsulation efficiency in the future. Here are some possible solutions and research priorities.

(1) Conduct in-depth clinical research to verify safety: for phytonutrients that have demonstrated therapeutic effects, the research focus should gradually shift from animal models to the clinical field. This necessitates conducting more extensive and in-depth clinical trials to comprehensively evaluate their safety across different populations, such as healthy individuals and patients with IBD. As for probiotics and prebiotics, given their existing clinical applications, it is imperative that we carefully screen and identify potential allergens before patients adopt these therapies. Furthermore, pharmacodynamic experiments regarding NGMMs should also be conducted to determine the selectivity and appropriate dosage of NGMMs for different populations.

(2) More mechanistic studies need to be conducted: specifically, further research is needed on the interaction between phytonutrients and gut microbiota, how phytonutrients exert their regulatory effects on gut microbiota and the impact of downstream signaling pathways triggered by the activation of

bile acid receptors by SBAs on inflammation and gut microbiota metabolism.

(3) Optimization of the preparation process: for hydrophobic NGMMs, in the process of constructing therapeutic systems, preference should be given to low-toxicity, non-toxic, or biocompatible organic solvents such as ethanol and glycerin, to reduce potential threats to patient health. Rigorous toxicity assessments should be conducted on the solvents used during the preparation process to ensure that the solvent residue levels are within safe limits. For probiotic-based therapeutic systems, since encapsulation strategies based on physical extrusion and electrostatic interactions may lead to decreased probiotic activity and leakage of probiotics, our future research focus should shift towards chemical modification and biological modification under mild conditions. Encapsulating probiotics through chemical forces or relying on metabolic processes of probiotics (such as biofilm formation and self-oxidation of surfaces) can better maintain their viability and improve encapsulation efficiency. Furthermore, from a technical perspective, the emergence of novel encapsulation technologies such as microfluidic technology offers brand-new options for achieving efficient and safe encapsulation of probiotics.

(4) Developing personalized treatment plans: due to the varying compositions of intestinal microbiota and metabolic characteristics among different patients, it is crucial to develop personalized treatment plans. This involves selecting appropriate types and doses of NGMMs based on the specific circumstances of each patient. During the treatment process, it is essential to regularly monitor changes in the patient's intestinal microbiota, health status, and any potential side effects, to promptly adjust the treatment plan as necessary.

NGMMs have demonstrated significant regulatory capabilities for gut microbiota, and their natural origin and ease of access grant them a unique advantage in the treatment of IBD. The development of therapeutic systems based on NGMMs can maximize their efficacy and overcome the limitations of using NGMMs in IBD treatment. In the future, the therapeutic system based on NGMMs should continue to evolve towards greater safety and efficacy. The current limitations faced by NGMMs will be addressed with deeper research into their mechanisms and the development of novel encapsulation technologies. The therapeutic systems based on NGMMs hold promise as a novel option for treating IBD through modulation of the gut microbiota.

Data availability

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

Conflicts of interest

There are no conflicts to declare.

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