Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

Research advances on encapsulation of probiotics with nanomaterials and their repair mechanisms on intestinal barriers

Xiaochen Wang[a,1], Mengxi Yu[a,1], Jianming Ye[a,1], Ting Liu[a], Lijuan Jian[a], Xiaoyan Zheng[b], Yuan Wang[a,c,d], Wei Song[a,c,d], Yane Luo[a,c,*], Tianli Yue[a,c,d]

[a] College of Food Science and Technology, Northwest University, Xi'an 710069, China
[b] College of Chemical Engineering, Northwest University, Xi'an 710069, China
[c] Laboratory of Nutritional and Healthy Food-Individuation Manufacturing Engineering, Xi'an 710069, China
[d] Research Center of Food Safety Risk Assessment and Control, Xi'an 710069, China

ARTICLE INFO

Article history:
Received 7 January 2023
Received in revised form 15 February 2023
Accepted 15 May 2023

Keywords:
Probiotics
Encapsulation
Environment-responsive release
Repair mechanisms
Selective colonization

ABSTRACT

Probiotics participate in various physiological activities and contribute to body health. However, their viability and bioefficacy are adversely affected by gastrointestinal harsh conditions, such as gastric acid, bile salts and various enzymes. Fortunately, encapsulation based on various nanomaterials shows tremendous potential to protect probiotics. In this review, we introduced some novel encapsulation technologies involving nanomaterials in view of predesigned stability and viability, selective adhesion, smart release and colonization, and efficacy exertion of encapsulated probiotics. Furthermore, the interactions between encapsulated probiotics and the gastrointestinal tract were summarized and analyzed, with highlighting the regulatory mechanisms of encapsulated probiotics on intestinal mechanical barrier, chemical barrier, biological barrier and immune barrier. This review would benefit the food and pharmaceutical industries in preparation and utilization of multifunctional encapsulated probiotics.

1. Introduction

The intestinal barriers are semipermeable with the largest surface in body, absorbing nutrients and responding immune reactions, while limiting the transport of potentially harmful antigens and microorganisms[1-2]. Their integrity is critical to our survival, health and defense. However, damage occurs when the intestinal barriers are chronically exposed to alcohol, high fat, high sugar and other adverse environments due to poor diet[3-4]. The damaged intestinal barriers may trigger uncontrollable immune response and cannot remain the intestinal microbiota homeostasis, leading to intestinal inflammatory diseases, extraintestinal autoimmune diseases (such as rheumatoid arthritis and multiple sclerosis) and metabolic diseases (such as diabetes and obesity)[5]. Correspondingly, repairing intestinal wall, restoring mucosal thickness, reconstructing microbiota homeostasis and balancing inflammatory factors are necessary to restore the intestinal health.

The recovery of intestinal integrity are mainly involved in the reconstruction of cytoskeleton, the migration, proliferation and differentiation of intestinal epithelial cells, as well as the effect of various cell growth factors[6-7]. Normally, about 10^{11} epithelial cells are lost from the intestinal cavity every day, which is supplemented by the proliferation and differentiation of intestinal stem cells. Besides, the intestinal microbiota that can also form additional mucus and immune layers to protect the intestinal mechanical barrier[8-9], with clearing up pathogens, pollutants and other harmful substances[8-10]. As to immune layer, intestinal microbiota mainly participates in

[1] The authors contributed equally.
[*] Corresponding author at: College of Food Science and Technology, Northwest University, Xi'an 710069, China.
E-mail address: luoyane@nwu.edu.cn (Y.E. Luo)
Peer review under responsibility of Tsinghua University Press.

Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2022.9250246

the secretion of antimicrobial peptides and stimulates the formation of interleukin (IL)-10, IL-17, IL-22, etc.[11]. With further research, the interactions between intestinal microbiota and host are found to benefit the maturation and maintenance of healthy mechanical barrier, the reconstruction of microbiota homeostasis and the development of immune system[12-13].

Both types of microorganisms i.e., pathogens and probiotics are present in the intestine. Among them, probiotics such as *Lactobacillus rhamnosus* 1.0320 and *Lactobacillus paracasei* HII01, can improve the *in vivo* defense system by increasing the number of beneficial microbes, inhibiting the growth of harmful ones, and modulating the diversity of microbial communities[14-15]. Meanwhile, *Lactobacillus brevis* LB062, *L. brevis* LB068 and *Lactobacillus fermentum* LF06 produce antibacterial substances and acidic metabolites to prevent the adhesion and proliferation of pathogenic bacteria in the gastrointestinal tract[16]. In recent years, probiotics have become one worldwide research hotspot, being applied in the treatment of some diseases involving skin[17], oral cavity[18], gastrointestinal tract[19], vagina[20]. Whereas, oral probiotics are often seriously damaged by gastric acid and bile salt in the gastrointestinal tract. Continuous peristalsis of the gastrointestinal tract will also accelerate the removal of probiotics from the intestinal tract[21]. Some pathological microenvironments of the diseased intestine are enriched with reactive oxygen species (ROS) that can strongly oxidize the lipid and protein of probiotics, causing cell-wall damage and promoting programmed death of probiotics[22-23]. Moreover, the intestinal mucosal barrier is often destroyed by inflammation, leading to too low content of mucins to support the adhesion of probiotics[24-25]. And thus, oral probiotics are not easy to colonize in the mucus layer, and part of them may even enter into blood through the damaged intestinal barriers with increasing the risk of bacterial translocation[26-27]. Generally, the damaged intestinal barriers greatly impair the colonization and biological efficacy of oral probiotics.

In order to overcome the adverse conditions mentioned above, some technologies about surface modification and encapsulation of probiotics are developed[28-29]. In which, encapsulation with nanomaterials has attracted more attention due to its advantages, such as stimulus responsibility, multimodal controlled release and high mechanical performance[30-31]. At present, most researches are focused on encapsulation technology to improve probiotics' gastrointestinal tolerance, survival rate and bioactivity[32-33]. However, the influences of encapsulated probiotics on the gastrointestinal tract and their repair mechanisms are scarcely summarized and analyzed. Thereby, we focus on the preparation and *in vivo* roles of probiotics encapsulated by nanomaterials, especially introducing their repair function and steady-state regulation on intestinal four-layer barriers. This review might do favor to the efficient preparation and utilization of encapsulated probiotics to regulate intestinal barrier homeostasis and restore intestinal health.

2. Encapsulation technology of probiotics based on nanomaterials

Nanomaterials have been widely used to modify and encapsulate probiotics and other bioactive substances[32]. These nanomaterials can be categorized into nanoparticles[34], nanofibers[35] and nanofilms[36] in view of shape (Fig. 1). Encapsulation technology of probiotics based on various nanomaterials are listed in Table 1.

Table 1
Current encapsulation technology of probiotics based on various nanomaterials.

Nanotechnology	Strains	Material 1	Material 2	Preparation methods	Encapsulation mechanisms	References
Metal nanoparticles	*L. plantarum*	Fe_3O_4	Pectin	Mechanical stirring	Electrostatic attraction	[38,155]
	Pediococcus pentosaceus Li05	MgO	Alginate-gelatin	Electrostatic microencapsulation unit	Hydrogen bond, electrostatic attraction, coordination compound	[156-157]
Polymer nanoparticles	*L. plantarum*	Cellulose fiber	Cellulose nanofiber	Mechanical stirring	Electrostatic attraction	[158]
		Pectin	Starch	Mechanical stirring	Hydrogen bond	[159-160]
		Grafting sodium polyacrylate from alginate	Alginate	Mechanical stirring	Calcium ions crosslink	[161]
	L. reuteri	Carboxymethyl konjac glucomannan	Chitosan	Mechanical stirring	Hydrogen bond electrostatic attraction	[162]
	L. rhamnosus	Alginate	Chitosan	Mechanical stirring	Electrostatic attraction	[163]
		Alginate	–	Mechanical stirring	Calcium ions crosslink	[75]
Liposome	*L. rhamnosus*	Lecithin	Chitosan- fish skin	Mechanical stirring	Electrostatic attraction	[37,164]
	E. coli Nissle 1917	Pt	mPEG-DSPE	Mechanical stirring	–	[55]
		Dioleoylphosphatydic acid	Cholesterol	Mechanical stirring	Self-assembly	[34]
Nanofiber	*L. plantarum*	Polylactic acid	–	Coaxial electrospinning	Hydrogen bond	[165-166]
	L. acidophilus	Gum Arabic	Polyvinyl alcohol	Electrospinning	Hydrogen bond	[61]
	L. rhamnosus, *L. acidophilus*, *L. plantarum*	Gum Arabic	Pullulan	Electrospinning	–	[167]
	Bifidobacterium animalis Bb12	Chitosan	Poly (vinyl alcohol)	Electrospinning	Hydrogen bond	[168-169]
	Lactobacilli bifidobacteria	Sodium alginate	Corn starch	Electrospinning	Hydrogen bond	[170-171]
Nano coating	*L. acidophilus*	Chitosan	Sulfated β-glucan	Mechanical stirring	Electrostatic attraction	[172-173]
		Oligosaccharides	Sodium alginate	Mechanical stirring	Schiff-base reaction	[174]
	E. coli Nissle 1917	Tannic acid	$FeCl_3{\cdot}6H_2O$	Mechanical stirring	Coordination compound	[41,175]
		Tannic acid	$FeCl_3$ and Eudragit L100	Co-culture	Coordination compound	[68,176]
Biofilm encapsulation	*L. rhamnosus*	Polydopamine		Mechanical stirring	Hydrogen bonding	[40]
	L. plantarum	Protein BslA	Protein TasA	Co-culture	Self-assembly	[73]
	L. acidophilus, *L. casei*, *L. rhamnosus*	Alginate	–	Mechanical stirring	Calcium ions crosslink	[74]
	S. boulardii	Alginate	–	Co-culture	Calcium ions crosslink	[177]

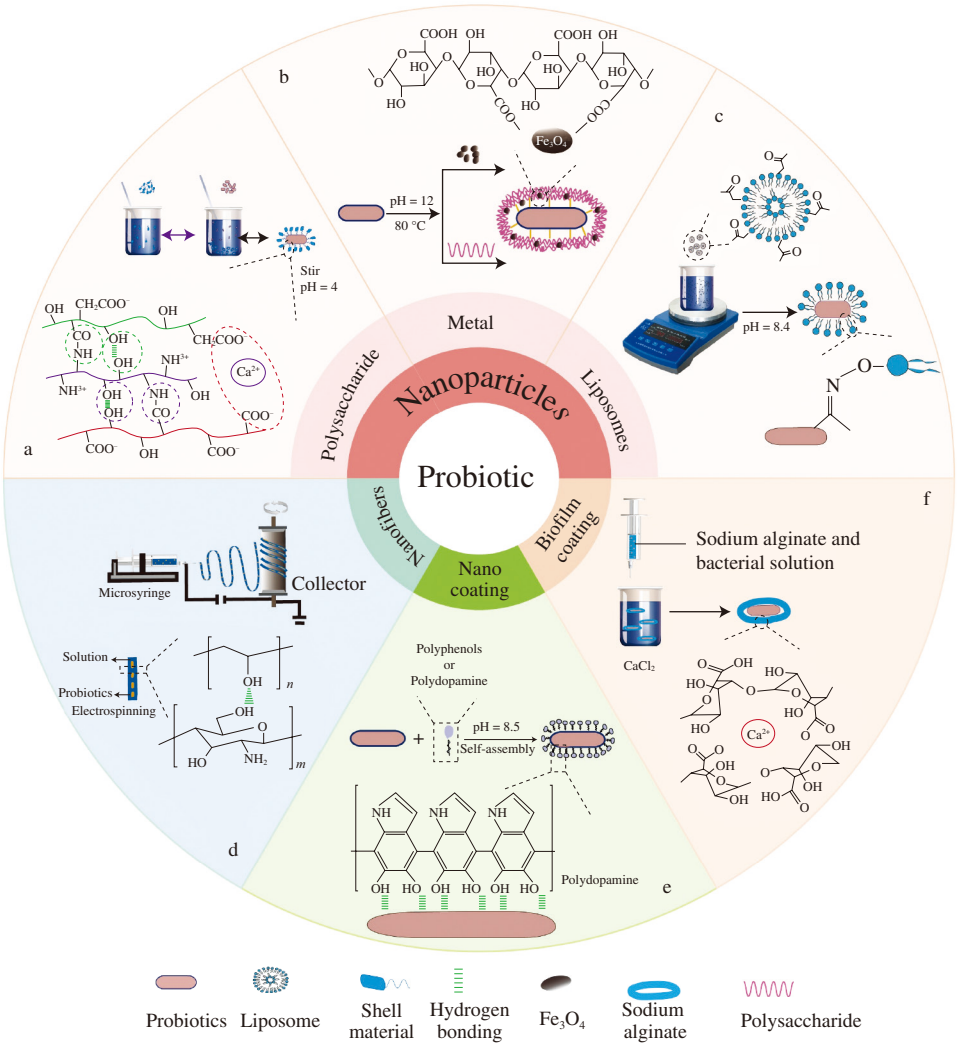

Fig. 1 Encapsulation technology of probiotics based on various nanomaterials. (a) Polysaccharide-based nanoparticles, synthesized by sodium alginate, chitosan and konjac glucomannan, are used to entrap *L. reuteri*[162]; (b) Metal nanoparticles, composed of pectin and ferric oxide, are utilized to wrap *L. plantarum*[38]; (c) Liposomes are applied to capsulate *E. coli* Nissle 1917[34]; (d) Nanofiber, based on chitosan and polyvinyl alcohol, is used to encapsulate *Bifidobacteria*[168]; (e) Nano coating is formed by depositing polydopamine on the surface of *L. rhamnosus*[36]; (f) Bio-membrane, mainly consisted of alginate, is applied to encapsulate *L. plantarum*[74].

2.1 *Nanoparticles*

To solve the problems associated with stability, safety, targeted adhesion and colonization, some nanoparticles, such as liposomes, iron and polysaccharide nanoparticles, have been used to encapsulate probiotics[37-39]. Meanwhile, the surfaces of nanoparticles are frequently modified by ligands or functional materials for targeted delivery, environmentally responsive release and high bioavailability of probiotics[40-43].

2.1.1 *Metal nanoparticles*

Because some complicated surface modifications are needed to improve the aqueous dispersion of metal nanoparticles, only a few have been developed to encapsulate probiotics. In which, iron oxide (Fe_3O_4) nanoparticles approved by the FDA have been tried to coat probiotics. To resist the dissolution of saliva and gastric juice, pectin is adsorbed on the surface of Fe_3O_4 nanoparticles to form iron-pectin nanoparticles[38]. This encapsulation technology is simple, just mixing Fe_3O_4 nanoparticles with pectin solution that is prepared from orange peel and contains probiotics under continuous stir for 60 min[38]. Consequently, the number of viable probiotics coated by iron oxide nanoparticles only decreased by 0.85 (lg (CFU/mL)) after 60 days of storage[38].

2.1.2 *Polysaccharide-based nanoparticles*

Some natural or synthetic polymers have been applied in the encapsulation of probiotics. Chitosan (CS), a polycationic natural polysaccharide, is a landmark material for the preparation of polymer nanoparticles. Chitosan nanoparticles (CSNPs) are synthesized mainly through ionotropic gelation, emulsification solvent diffusion, and microemulsion, etc.[44]. Ionic gelation involves the interaction between ionic polymers and cations or anions to form cross-linked structures. For example, the amine groups of chitosan make it a cationic polymer that can interacts with anionic polymers[45]. Emulsification solvent diffusion method can obtain an oil-in-water emulsion after high pressure homogenization by mixing organic phase into a solution of stabilizer and chitosan. After that, a large amount of water dilutes the emulsion to diffuse the organic solvent, and the polymer is

precipitated with forming nanoparticles[46]. As to microemulsion method, glutaraldehyde (crosslinking agent) and chitosan in acetic acid solution are added to surfactants. The mixture is stirred overnight at 25 °C to complete the crosslinking between amine groups of glutaraldehyde and chitosan. This crosslinking in presence of surfactant leads to the formation of nanoparticles[47].

In comparison to bulk CS, CSNP-based delivery system has a greater specific surface to adhere on both cells and mucosa[48-50]. Additionally, CSNPs can improve the bioavailability and tolerance in harsh environment of probiotics[51-52]. For example, CSNP and alginate are used to encapsulate probiotic *E. coli* Nissle 1917 (EcN), and this encapsulated EcN can effectively adhere to HT-29 cells in the intestine with reducing the invasion of jejunum bacteria[53].

2.1.3 Nanoliposomes

Liposomes are mainly prepared by self-assembly of phospholipids and cholesterol, the preparation process is simple and efficient, and the targeted product has good biocompatibility. At present, there are two methods for encapsulating probiotics by nanoliposomes. The simplest method is to prepare liposomes by membrane dispersion method first, and then mix liposomes and bacteria suspension to obtain single-cell encapsulated probiotics[54].

Besides, the stability of nanoliposomes can be improved by adsorbing polysaccharides, proteins and metal nanoparticles onto the surface through electrostatic interactions. For instance, Pt nanoparticles can be embedded into mPEG-DSPE (i.e., polyethylene glycol derivatives of distearyl phosphatidylethanolamine) lipid nanomembrane to form platinum lipids for further encapsulating EcN under vortex, with obtaining encapsulated probiotic Pt-Lipid@EcN[55]. Due to platinum lipid protection, these encapsulated probiotics can resist the harsh environment *in vivo* after oral administration.

2.2 Nanofibers

Nanofibers have uniform morphology and composition, large surface area and high porosity, and they are often used to encapsulate various microorganisms, cells, genes and proteins[56]. Electrospinning technology is usually used to make nanofibers with materials such as polyvinyl alcohol, polyethylene oxide, cellulose and chitosan[57]. The encapsulation of probiotics within nanofibers can improve the stability of probiotic cells and realize site-specific delivery. For instance, ultrathin polyvinyl alcohol electrospun fibers for wrapping *B. animalis* Bb12 have an average diameter of 150 nm, they can effectively maintain the viability of encapsulated probiotics after 40 days of storage at room temperature or 130 days under refrigeration[58]. Polyvinyl alcohol nanofibers encapsulating *L. rhamnosus* CRL1332 have an average diameter of 95 nm and can maintain bacterial activity after 360 days of deoxygenation storage at 4 °C[35]. In addition, nanofiber-immobilized *L. rhamnosus* can still inhibit urogenital pathogens.

During nanofiber formation, excipients can effectively reduce the loss of *L. paracasei* activity[59]. When using Eudragit® L100 (methacrylic acid, a film forming material used for oral tablets and capsules) and sodium alginate to encapsulate *L. paracasei* by electrospinning, the Eudragit® L100 electrospun fibers can provide a hydrophobic environment for *L. paracasei*, protecting them from oxygen to preserve their viability[60]. *L. acidophilus* wrapped in nanofibers made from gum arabic and polyvinyl alcohol remained 63.99% of survival rate after lying in simulated gastrointestinal tract for 2 h, while all free ones were dead[61]. If *L. rhamnosus* were encapsulated in three-layer nanofibers, inner-layer constructed by hydrophilic amylopectin and outer-layer constructed by hydrophobic polylactic acid and glycolic acid, their survival rate was 72% after entering into the small intestine for 72 h[62].

2.3 Nanofilms

2.3.1 Nanofilm prepared by nanocoating technology

Nanocoating is a single-cell encapsulation technology that not only protects probiotics, but also confers some usefully exogenous properties to probiotics. Nano-film is formed by molecular self-assembly based on non-covalent interactions between molecules, such as hydrogen bonds[63]. Polydopamine biomimetic nanofilm is inspired by mussels[64]. Viscous proteins secreted by mussels have a large number of dopa which can be assembled into polydopamine on the surface of probiotics to form nanofilm[40]. Compared with free EcN, the survival rate of EcN encapsulated by polydopamine was increased by 6 times in the stomach, and the retention rate in the intestine was increased by more than 30 times[36]. Silk fibroin can also self-assemble on the surface of bacteria to form a complete and stable nanofilm through salting-out process[65]. This nanofilm not only protects probiotics from damage, but also maintains their ability to proliferate. Meanwhile, silk fibroin has anti-inflammatory activity, synergistically enhancing the therapeutic effects of probiotics on intestinal mucositis[65].

Polyphenols possessing multiple pyrocatechol groups are an ideal material to self-assemble into nanofilm, with good antibacterial and adhesion properties[66]. Metal-polyphenol supramolecular network, formed by coordination of metal and polyphenols, has been widely used in nanomedicine, catalysis, environment and other fields. In addition to dopa, the other natural polyphenols such as tannic acid (TA) and caffeic acid (CA) have been exploited to encapsulate probiotics[67]. At present, the most common nano-coating technology for probiotic encapsulation is based on crosslink between trivalent iron ions and TA[41]. First, iron ions and TA formed coordination bonds and self-assembled on the surface of EcN to form the first dense mucosal adhesion layer TA-EcN; and then, calcium ions and Eudragit L100 self-assembled on the surface of TA-EcN to form a second layer[68]. The Eudragit L100 layer protected EcN from gastric juice but broke down in the intestine (pH > 6); the TA layer improved the adhesion of probiotics onto the intestine barriers and subsidiarily exerted the therapeutic effect of tannic acid on colitis[68].

2.3.2 Nano-biofilm

In nature, some bacteria surviving in the extreme harsh conditions usually form their own biofilms[69]. Probiotics such as *Bacillus subtilis* secrete extracellular polysaccharides, lipids and proteins during their growth and proliferation[70-71]. These sticky substrates are assembled into biofilms that not only significantly improve the tolerance of *B. subtilis* to gastric juice and bile acids[72], but also provide protection for other probiotics such as *L. plantarum*[73]. The exopolysaccharide of

B. subtilis bundles the colony, Bs1A protein forms a hydrophobic layer, and TasA protein self-assembles and anchors to the cell wall to form biofilm-encapsulated probiotics. The viable counts in simulated gastric and intestinal fluids were increased by 0.86 and 0.9 (lg (CFU/mL)), respectively[73]. If *L. plantarum* is embed in alginate, a crucial component of *Pseudomonas*' biofilm, a polyanionic nano-shell will be formed to resist the gastrointestinal tract environment and the damage caused by cationic antibiotics[74-75]. Interestingly, probiotics will continue to proliferate within biofilms and then break out to become free cells[76]. Thereby, the limited life cycle of nano-biofilm should be taken into consideration in future applications[77]. Being similar to nano-coating technology, nano-biofilm encapsulation is also commonly served to parcel single cell.

3. Selective colonization of probiotics encapsulated by nanomaterials

During preparation of encapsulated probiotics, their selective adhesion and colonization should be well considered according to the physicochemical properties of various nanomaterials.

3.1 Selective colonization based on TA and metal ion complex

In order to increase the retention time of probiotics in the intestine, TA is widely utilized in encapsulation process[41]. TA is a secondary metabolite produced by microorganisms and plants, with a molecular weight around 500–3 000 Da. Because catechol groups of TA can form hydrogen bonds, covalent bonds and/or π–π interactions with different substrates, TA exhibits strong adhesion properties[78]. For instance, multiple TA monomers react with Ca^{2+} for forming a nanofilm-like assembly on the surface of EcN to adhere to mucin[79].

When TA-metal ion complex and Eudragit L100 (an enteric polymer) were used to encapsulate EcN in turn for forming layer-by-layer LbL encapsulated EcN, which that can enhance tolerance to harsh environments in the upper digestive tract as well as special adhesion to the intestinal mucosa, and even realize colonization of probiotics[68].

Additionally, the inner assembled TA nanofilm can remove ROS in the pathological environment of inflammatory bowel diseases (IBD) and further improve the survival rate of probiotics[80]. TA can also be used to self-assemble with poloxamer 188 (F68, an intravenous excipient), forming a TA@F68 nanoshell to encapsulate EcN (Fig. 2A)[80].

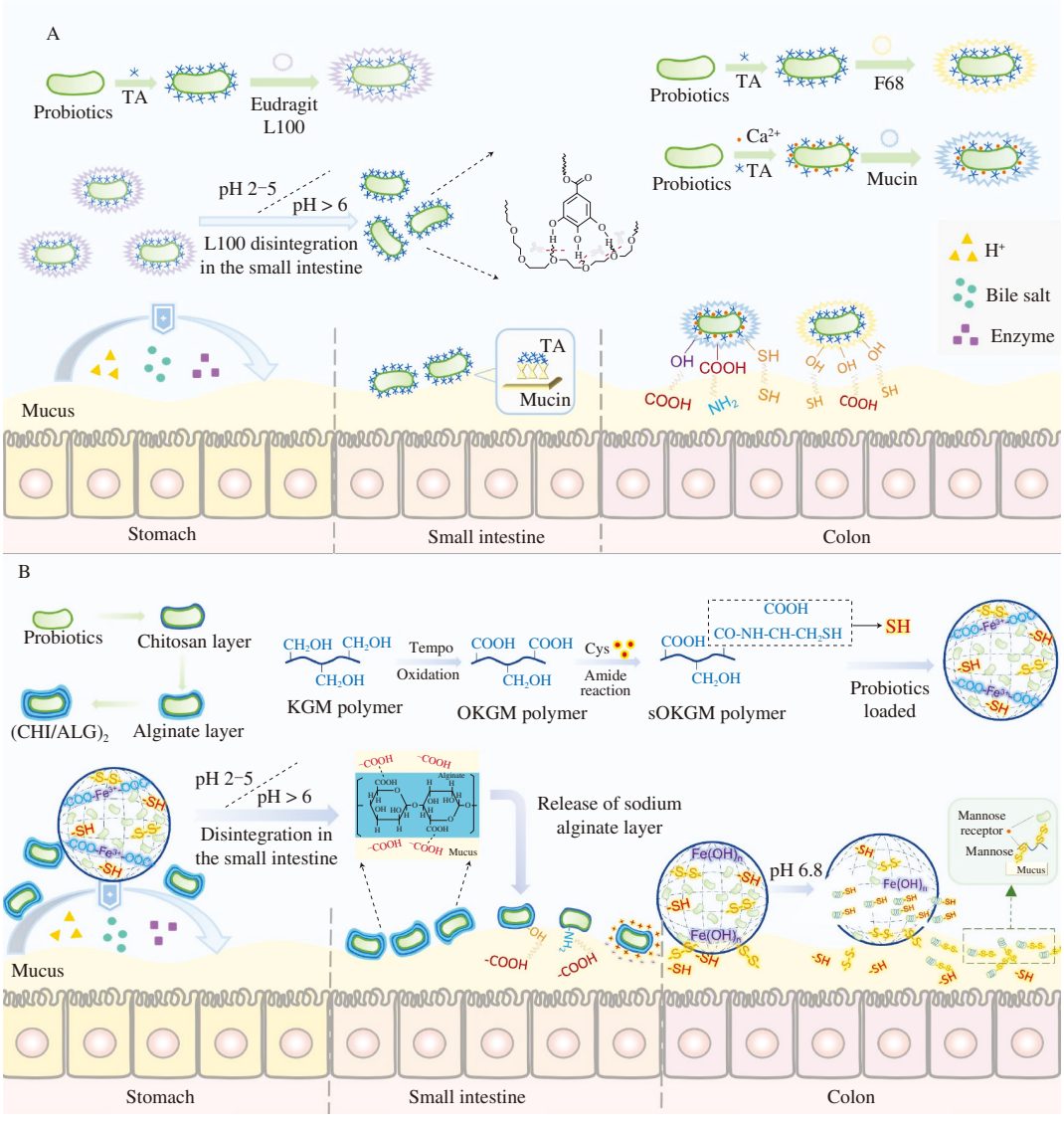

Fig. 2 Selective colonization of encapsulated probiotics by TA and polysaccharide. (A) Tolerance of probiotics encapsulated by TA assembly in the stomach and the targeted colonization in the intestine[68,79-80]. (B) Tolerance of probiotics encapsulated by various polysaccharides in the stomach and the targeted colonization in the intestine[84,91].

3.2 Selective colonization based on polysaccharides

Chitosan and sodium alginate are biodegradable polysaccharides with good biocompatibility and unique adhesion properties[81]. In which, chitosan is positively charged and interacts with intestinal mucin via electrostatic attraction, hydrogen bond and hydrophobic effect[82]; alginate is an anionic polymer with abundant carboxyl groups to adhere to mucosa via hydrogen bonds[83]. During LbL encapsulation, cationic polysaccharide-chitosan (CHI) can be designed as inner nanofilm for *Bacillus coagulans* (BC), with anionic polysaccharide-alginate (ALG) acting as outer layer. In order to protect probiotics from gastrointestinal tract insults and facilitate both muco-adhesion and direct growth on intestinal surface, three-layer nanoshells $(CHI/ALG)_3$ are designed to obtain (CHI/ALG)-LbL BC (Fig. 2B)[84]. After intake of three-layer encapsulated BC, LbL degradation will appear in the intestine. With the degradation of outer sodium alginate layer, the chitosan layer is exposed and exerts its adhesion property to achieve sustainable colonization of BC.

Glycoproteins in intestinal mucus contain large amounts of cysteine, which is also abundant in the outer membrane of Gram-negative bacteria and cellular protein layer[85-87]. Thiopolymers can form disulfide bonds with cysteine, and thus they can serve as intermediate junctions between probiotics and the intestinal mucosa[88-89]. Moreover, sulfated chitosan can increase viscosity by 100 times than unmodified chitosan[90]; thiochitosan outer nanofilm can also significantly enhance the adhesion and colonization of *Lactobacillus evansi* DPC16 on the surface of colon[48]. Thiooxidized Konjac glucomannan (sOKGM), i.e., oxidized Konjac glucomannan (OKGM) conjugated by cysteine via carboxyl groups, can also protect *Bifidobacteria* from gastric acids and provide good adhesion and colonization in the colon (Fig. 2B)[91].

3.3 Selective colonization based on amino acids and their derivatives

Amino acid-based modification has recently been regarded as one of the most powerful methods for gut microbes[92-93]. *D*-amino acid is an important element of the bacterial cell walls and can be developed into fluorescent probe[94-96]. *D*-amino acid labeling probe has a good tolerance and can efficiently and rapidly label bacteria, which is useful to study intestinal microflora[97]. The unnatural

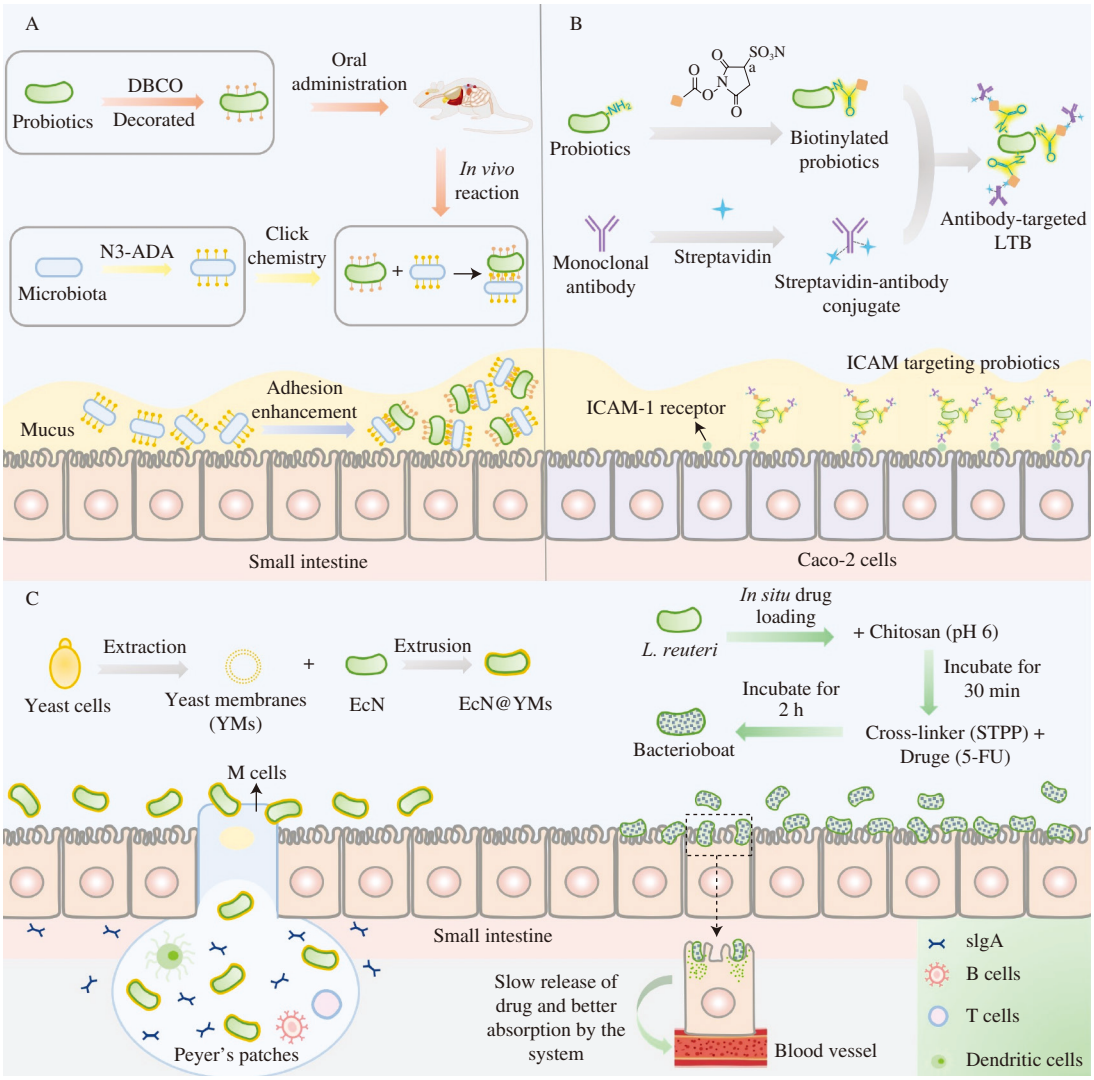

Fig. 3 Selective colonization of encapsulated probiotics based on amino acids, their derivatives and biofilms. (A) Bio-orthogonal mediated bacterial delivery enhancing probiotic colonization in the intestine[42]. (B) Preparation and the intestinal colonization of antibody-streptavidin-biotinylated probiotics[43]. (C) Preparation and the intestinal colonization of probiotics encapsulated by bacterial membrane[103-104]. N3-ADA, Azido-modified D-alanine; LTB, Live therapeutic bacteria.

D-amino acids can also be used for precise bacterium detection and therapy[98-99]. Probiotics to be delivered were modified with dibenzocyclooctyne (DBCO) through amide bonds (Fig. 3A). After oral administration of DBCO-modified probiotics, a bio-orthogonal reaction occurred between probiotics and intestinal residents of mice, to significantly improve the colonization efficiency of probiotics[42]. Similarly, in colitis mice induced by dextran sulfate sodium (DSS), bio-orthogonally mediated *C. buturicum* can be effectively colonized.

Due to the specific interactions between biotin and streptavidin, they can form a synthetic adhesin widely used in biological coupling reactions[100]. *N*-Hydroxysuccinimide ester can simultaneously connect biotin and amines on the surface of bacteria, forming biotin-modified bacteria. And then streptavidin specially binds biotin-modified *Lactobacillus* and the monoclonal antibody against intracellular adhesion molecule (aICAM-1), this complex subsequently bonds the ICAM-1 receptor secreted on the surface by Caco-2 cells (Fig. 3B). This method based on specific binding of functional groups can significantly improve the colonization ratio of probiotics in the intestine[43].

3.4 Selective colonization based on bacterial biofilms

The biofilm consists of a mixture of various type of polysaccharides and proteins, it has been exploited to transport drugs, small molecules and macromolecules to intestinal microvilli. Biofilm can serve as a binder to attach bacteria onto the surface of the intestinal wall as well as prevent bacteria from clearance by flowing liquid[101-102]. Biofilm can also play a role in targeted release of probiotics. For example, *β*-glucan in yeast membrane can be recognized and swallowed by micro-folded cells. Therefore, encapsulated EcN by yeast membrane through physical extrusion not only improves their tolerance to the harsh gastrointestinal environments, but also enables themselves to enter into the Pellet with improving immune response and maintaining intestinal homeostasis[103]. Besides, the bioavailability of oral *B. subtilis* encapsulated by self-biomembrane was 125 times higher than that of free *B. subtilis*, and the intestinal colonization rate was 17 times higher in living pigs[72].

A novel bacterial carrier i.e., bacterial boat for oral administration was prepared by encapsulating *Lactobacillus reuteri* via *in-situ* and *ex-situ* methods with mesoporous nanoparticles (Fig. 3C). The glycoprotein secreted by *L. reuteri* are specially absorbed by the intestinal microvilli to prolong colonization span of probiotics in the intestine[104].

4. Environment-responsive release of encapsulated probiotics

4.1 Probiotic release based on pH-responsive

Since pH value of the gastrointestinal tract changes significantly, the degradation of out-layer polymers encapsulating probiotics can be designed to trigger by pH change[105]. This out-layer degradation mainly relies on chemical reactivity of the side chains and functional groups in the main chain of the polymers, and swelling-deswelling can be controlled by electrostatic repulsion (i.e., ionic strength) to achieve pH response and probiotic release.

Alginate is a linear polysaccharide composed of (1-4)-*β*-*D*-mannuronic acid (M) and (1-4)-*α*-*L*-guluronic (G) residues. Under the action of divalent cations such as calcium chloride, alginate can be assembled into pH-sensitive cross-linked complex which is beneficial to slowing down the infiltration of gastric acid and increasing the release of probiotics in the intestine[106-107]. However, the instability of alginate greatly limits its application. For instance, alginates are sensitive to acidic media, such as gastric juice[108], leading to unexpected release of encapsulated probiotics[109]. The other polymers are introduced to solve this problem via coating alginate gel, such as chitosan[110]. Compared with alginate alone, chitosan-coated alginate increased the survival rate of *L. plantarum* in simulated gastric fluid (pH 1.5) by 0.5–2 logs[111], at the cost of decrease of release rate in the small intestine[112].

In order to realize the targeted release of encapsulated *Lactobacilli* in intestinal tract, a novel intestinal targeted Ca-alginate (CA) carrier have been successfully developed. The carrier possessing a core-shell structure, i.e., an inner core of CA gel encapsulating bacteria and an outer shell composited of calcified alginate-protamine (CAP), can protect of encapsulated probiotics in the stomach and release probiotics in the small intestine in a pH-responsive model[108]. As a cationic polypeptide, protamine interacts with CA network molecules via electrostatic pull, with enhancing the stability of alginate. Milk proteins can also combine alginate with synthesizing a denser hydrogel to reduce the permeability of encapsulated probiotics[113], and then the survival rate of *L. acidophilus* in simulated gastric fluid is increased by 40%[114].

4.2 Probiotic release based on specific enzymatic hydrolysis

The colonic microbiota produce a variety of enzymes to ferment carbohydrates in the chyme, such as *β*-*D*-galactosidase, *β*-xylosidase, *β*-*D*-glucosidase and *α*-*L*-arabinosidase[115], which are responsible for the degradation of polysaccharides in the colon to meet the energy needs of bacterial survival and propagation[116].

Natural polysaccharides such as chitosan have good tolerance to enzymes in the stomach and small intestine, but they can be specifically hydrolyzed by *β*-glucosidase produced by colonic microbes. In addition, positively charged chitosan can interact electrostatically with negatively charged gastrointestinal mucosal surfaces and is considered to be an effective mucosal adhesive[117]. Therefore, chitosan is often used as a colon-specific enzymatic hydrolysis material to realize targeted release of probiotics[118]. However, the encapsulation efficiency is poor when chitosan is used alone, so it is mainly used as shell[119]. Pectin has also become a promising biopolymer that can be used to construct microbe triggered colon-specific carriers. Pectin is not sensitive to upper digestive enzymes, but is easily degraded by colon enzymes when it reaches the colon. Similar to alginate, when the pectin solution is squeezed into a medium containing concentrated calcium salt, a gel can be formed also. Furthermore, pectin-based carriers can reduce the release of encapsulated probiotics in the gastrointestinal tract by secondary crosslinking, achieving targeted colonic release[120-122].

4.3 Probiotic release based on specific intestinal metabolites

Hyaluronic acid (HA) has abundant functional groups, including carboxyl and hydroxyl groups, which can be used for chemical

modification. Its repeated disaccharide units and high viscosity are conducive to its self-crosslinking to form supramolecular hydrogels[123]. The hydrogel has redox response characteristics and degrades when encountering hydrogen sulfide excreted by intestinal pathogens. Therefore, thiolated self-crosslinking hyaluronic acids can be used to prepare novel intestinal-targeted release hydrogels[124]. For instance, the HA−SH self-cross-linking hydrogel was used to encapsulate *L. rhamnosus*[125].

5. Repair mechanisms of intestinal four-layer barriers by probiotics

5.1 Repair of mechanical barrier

For enteric pathogens, adhesion to the intestinal epithelial cells is a critical step during infection. Pathogens invade the intestinal mucosal barrier by phagocytizing antigen-presenting cells (dendritic cells, microfolded cells), direct invasion of intestinal epithelium, or the paracellular pathway after disrupting cellular connections between epithelial cells. Fortunately, *Lactobacillus* can inhibit the adhesion of pathogens, thereby protecting the integrity of cell junctions and mucosal barriers[126]. *L. plantarum* ZLP001 significantly inhibited the increase of intestinal permeability induced by enterotoxigenic *E. coli* (ETEC) and enhanced the resistance of intestinal epithelium by maintaining enough tight junction proteins[127].

Lactobacillus and *Bifidobacterium* can maintain functions of the intestinal epithelial barrier by regulating the permeability of between intestinal epithelial cells and the expression of zonula occludens-1 (ZO-1). Moreover, *L. casei* is found to increase the expression of TLR2 and p-Akt protein, indicating preventing cytokine-induced dysfunction of epithelial barrier through the PI3K/Akt signaling pathway[128].

In addition, probiotics can promote the secretion of peptides produced by intestinal goblet cells, improve intestinal mucosal repair, and thus contribute to maintaining the integrity of mucus barrier. For instance, *Bifidobacterium dentatum* can secrete acetate and other products to increase the level of MUC2 mucin in T84 cells, and secrete aminobutyric acid (GABA) to stimulate autophagy mediating calcium signal and MUC2 release. *L. rhamnosus* can increase the expression of *Muc2* gene in mouse colon, and the thickness of mucus layer are increased in an EGF receptor dependent manner[129]. Besides, *L. plantarum* CCFM734 and CCFMI 237 can prevent mucin degradation by up regulating the transcription of sulfotransferase encoded by GAL3ST-2[130].

5.2 Repair of bio-chemical barriers

The chemical barrier molecules secreted by small intestinal cells, such as bacteriostins, antimicrobial peptides (AMP), regenerative islet-derived 3 (Reg3) protein family and lysozyme, play a crucial role in the spatial separation of intestinal bacteria and intestinal epithelial cells. EcN induces the secretion of human β-defensin 2 by mediating nuclear factor-κB (NF-κB) and activator protein-1-dependent pathways[131-132]. *In vivo*, EcN protects intestinal cells from infection by *Salmonella* and *Candida albicans*[133]. *In vitro*, EcN has been found to inhibit the invasion of *Salmonella*, *Yersinia enterocolitica*, *Shigella flexneri*, *Listeria pneumophila* and *Listeria monocytogenes*[134-135].

Lactic acid bacteria, such as *L. acidophilus*, *L. rhamnosus* and *B. coagulans*, can protect the host against pathogens by producing bacteriocin, regulating immune and nonimmune defense, balancing intestinal microbiota, etc. More importantly, these probiotics can compete with pathogens for nutrients and occupation sites in the intestinal epithelium, thereby inhibiting pathogen adhesion and alleviating bacterial enteritis[136]. Lactic acid produced by lactic acid bacteria can inhibit the growth of some pathogenic microorganisms[137], such as *Helicobacter pylori*, *Shigella fradiae*, and *E. coli* by reducing environmental pH[138-141]. *L. plantarum* Bar10 can effectively inhibit the adhesion of *S. choleraesuis* and *E. coli* to Caco-2 cells[126]. Similarly, *L. paracasei* inhibits pathogenic *Salmonella* Enteritidis and *Streptococcus* to adhere Caco-2 cells (Fig. 4); furthermore, pre-incubation *L. paracasei* with Caco-2 cells before addition of *Salmonella* can further greatly reduce pathogens' adhesion efficiency[142].

It is well known that *Salmonella typhimurium* is a typical intestinal pathogen to produce H_2S, easily triggering bacterial enteritis. Fortunately, *L. rhamnosus* encapsulated by hydrogel specifically attaching the intestinal barriers can slow down *S. typhimurium* invasion. Detailly, when encapsulated probiotics are exposed to H_2S emitted by intestinal pathogens, disulfide bonds in the skeleton of outer hydrogel layer despondingly break down as soon as possible, with releasing probiotics to compete with pathogen *S. typhimurium* for binding sites[125].

5.3 Repair of immune barrier

Preventing the excessive production of proinflammatory factors and increasing the secretion of anti-inflammatory factors, are the main ways of probiotics to alleviate intestinal inflammation. When probiotics were used in septic mice induced by cecal ligation and perforation (CLP), it was found that probiotics could inhibit the polarization to M1 macrophages but promote the polarization to M2, so as to inhibit inflammation and control immune balance[143-144].

It is found that genomic DNA of *L. plantarum* affects lipopolysaccharide (LPS)-induced mitogen-activated protein kinase (MAPK) activation, NF-κB activation, TNF-α expression, interleukin-1 receptor-associated kinase M, and pattern recognition receptor. Stimulation of THP-1 cells using *L. plantarum* g-DNA revealed that the phosphorylation of MAPKs and NF-κB was significantly inhibited, and that the LPS-induced tumor necrosis factor (TNF)-α was also inhibited [145].

With regulating the inflammatory response induced by adherent-invasive *E. coli* (AIEC), *Lactobacillus* was found to reduce the secretion of the pro-inflammatory factor TNF-α but increase the secretion of the anti-inflammatory factor IL-10 by macrophages[146]. *Lactococcus* showed good anti-inflammatory effects in macrophage RAW264.7 cells and DSS-induced IBD mice[147]. In detailed, *L. lactis* ML2018 can reduce the production of NO in macrophage cells after stimulated by LPS; while oral administration of *L. lactis* ML2018 significantly inhibits the up-regulation of IL-1β, IL-6 and TNF-α of mice after injection of DSS[148].

6. Development trends of encapsulated probiotics

Oral administration is the most convenient and popular style to probiotics involved therapy. Some inorganic nanoparticles, such

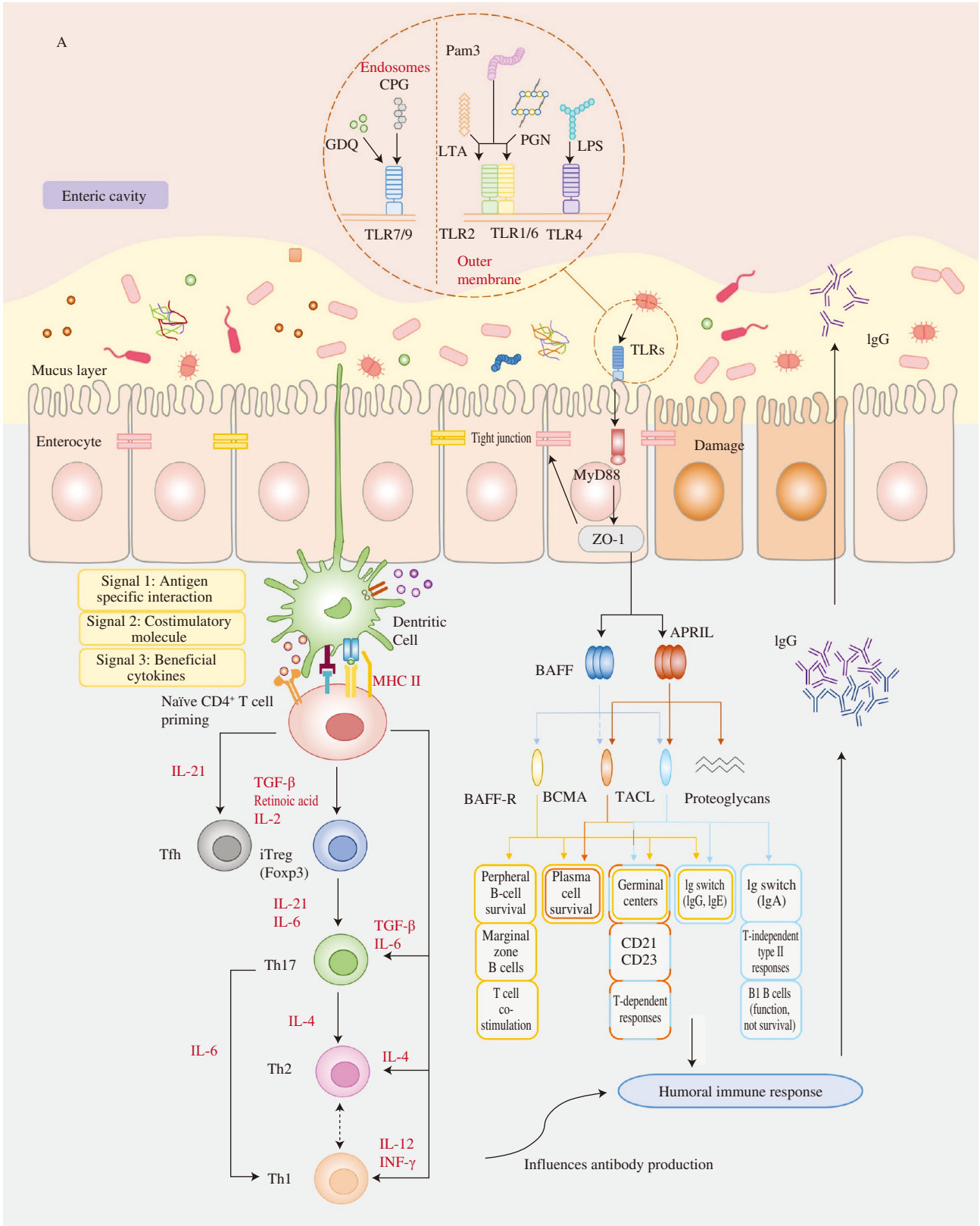

Fig. 4 Mechanisms of repair four-layer intestinal barriers by probiotics. (A) Intestinal epithelial cells initiate an immune response by recognizing harmful bacteria to prevent further disruption of the intestinal barrier. (B) Probiotics can enhance immunity, upregulating the anti-inflammatory cytokine production and inhibiting the production of pro-inflammatory cytokines. Neurotransmitters released by probiotics can modulate the gut brain axis through gut neurons, thereby reducing stress responses and improving anxiety-like behavior.

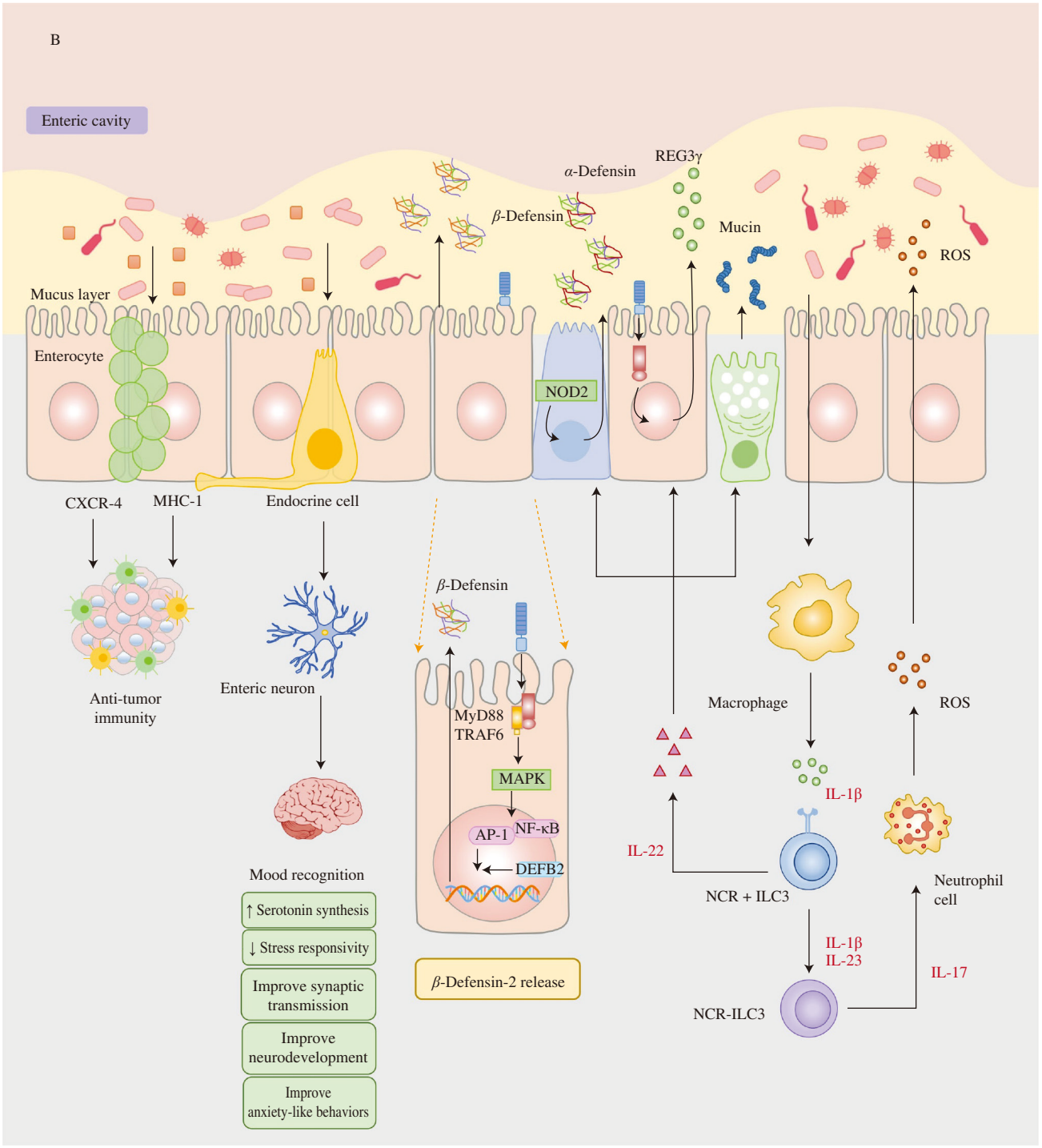

Fig. 4 (*Continued*)

as silver nanoparticles and zinc oxide nanoparticles, can regulate IBD microbiota to achieve well therapeutic effects[149]. However, long-term exposure to silver nanoparticles may lead to cell damage and inflammation through oxidative stress. Therefore, the other nanomaterials with good bio-compatibility and safety are screened out, such as various protein-based biopolymers, polysaccharides, lipids and synthetic polymers[150-151]. In addition, pH-sensitive polymers such as hydroxypropyl methyl cellulose phthalate, acrylate polymers, and cellulose acetate phthalate are widely used in formulations of enteric nanofilm, to minimize the contact of probiotics with gastric acid and reduce the loss of probiotic activity in the stomach[152].

The spore membrane might be developed into multifunctional coat nanoparticle (CN) via mechanical force, becoming a new material for the delivery of oral probiotics. Due to its high tolerance, excellent biocompatibility and natural affinity to some microbes, CN has been attempted to coat *B. subtilis* and *Bacillus licheniformis*[77]. Although CN can significantly increase survival, competitive colonization and proliferation of CN-coated probiotics (CN@BC) in the intestine, the germination efficiency of spores cannot be well

controlled and spore germination may disrupt ion homeostasis in the intestine[153-154]. It is urgent to understand the physicochemical properties, safety, bioavailability and efficacy of nanomaterials to ensure safe application of encapsulated probiotics[150].

At present, the preparation technologies of probiotic nanomaterials are more and more diversified, realizing the single-cell encapsulation and being potential to innovate probiotic delivery. Compared with bulk encapsulation, single-cell encapsulation can improve *in vivo* resistance, bioavailability and mucoadhesion, even potentially prevent and treat diseases at cellular level. Besides, single-cell encapsulation uses a small amount of initial material to produce bio-friendly nanofilm on probiotic cell through different biological and/or chemical engineering designs, without the need for acid-resistant microcapsules or complex processes.

7. Conclusion

The popular encapsulation technology of probiotics with nanomaterials as well as the excellent properties of encapsulated probiotics are summarized and systematically analyzed. Furthermore, repair mechanisms of the four-layer intestinal barriers are elucidated from repairing intestinal physical barrier, regulating chemical barrier, balancing biological barrier to enhancing immunity. With the advancement of nanotechnology in synthetic tools and biochemical characterization, encapsulation of probiotics will achieve greater development, benefiting the food and pharmaceutical industries in preparation and utilization of multifunctional encapsulated probiotics.

Declaration of competing interest

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

Acknowledgments

This work was financially supported by the National Key Research and Development Program (2019YFC1606704), the Key Research and Development Program of Shaanxi Province (2022NY-013), National Natural Science Foundation of China (31801653) and the Natural Science Foundation of Shaanxi Province (2019JQ-722).

References

[1] K.E. Barrett, New ways of thinking about (and teaching about) intestinal epithelial function, Adv. Phy. Edu. 32 (2008) 25-34. http://doi.org/10.1152/advan.00092.2007.

[2] M. Vancamelbeke, S. Vermeire, The intestinal barrier: a fundamental role in health and disease, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 821-834. http://doi.org/10.1080/17474124.2017.1343143.

[3] J. Gleeson, Diet, food components and the intestinal barrier, Nutr. Bull. 42 (2017) 123-131. http://doi.org/10.1111/nbu.12260.

[4] T. Suzuki, Regulation of the intestinal barrier by nutrients: the role of tight junctions, Anim. Sci. J. 91 (2020) e13357. http://doi.org/10.1111/asj.13357.

[5] C. Chelakkot, J. Ghim, S.H. Ryu, Mechanisms regulating intestinal barrier integrity and its pathological implications, Exp. Mol. Med. 50 (2018) 1-9. http://doi.org/10.1038/s12276-018-0126-x.

[6] M. Göke, M. Kanai, D.K. Podolsky, Intestinal fibroblasts regulate intestinal epithelial cell proliferation via hepatocyte growth factor, Amer. J. Phy-Gastro. Liver Phy. 274 (1998) G809-G818. http://doi.org/10.1152/ajpgi.1998.274.5.G809.

[7] A. Lan, F. Blachier, R. Benamouzig, et al., Mucosal healing in inflammatory bowel diseases: is there a place for nutritional supplementation? Inflamm. Bowel Dis. 21 (2015) 198-207. http://doi.org/10.1097/MIB.0000000000000177.

[8] P. Paone, P.D. Cani, Mucus barrier, mucins and gut microbiota: the expected slimy partners? Gut 69 (2020) 2232-2243. http://doi.org/10.1136/gutjnl-2020-322260.

[9] T. Takiishi, C.I.M. Fenero, N.O.S. Câmara, Intestinal barrier and gut microbiota: Shaping our immune responses throughout life, Tissue Barriers 5 (2017) e1373208. http://doi.org/10.1080/21688370.2017.1373208.

[10] Y. Goto, H. Kiyono, Epithelial barrier: an interface for the cross-communication between gut flora and immune system, Immunol. Rev. 245 (2012) 147-163. http://doi.org/10.1111/j.1600-065X.2011.01078.x.

[11] H.Y. Cheng, M.X. Ning, D.K. Chen, et al., Interactions between the gut microbiota and the host innate immune response against pathogens, Front. Immunol. 10 (2019) 607. http://doi.org/10.3389/fimmu.2019.00607.

[12] Y. Belkaid, T.W. Hand, Role of the microbiota in immunity and inflammation, Cell 157 (2014) 121-141. http://doi.org/10.1016/j.cell.2014.03.011.

[13] D. Zheng, T. Liwinski, E. Elinav, Interaction between microbiota and immunity in health and disease, Cell Res. 30 (2020) 492-506. http://doi.org/10.1038/s41422-020-0332-7.

[14] Z. Liu, F. Liu, W. Wang, et al., Study of the alleviation effects of a combination of *Lactobacillus rhamnosus* and inulin on mice with colitis, Food Funct. 11 (2020) 3823-3837. http://doi.org/10.1039/C9FO02992C.

[15] P. Toejing, N. Khampithum, S. Sirilun, et al., Influence of *Lactobacillus paracasei* HII01 supplementation on glycemia and inflammatory biomarkers in type 2 diabetes: a randomized clinical trial, Foods 10 (2021) 1455. http://doi.org/10.3390/foods10071455.

[16] X. Zhang, G.A. Esmail, A.F. Alzeer, et al., Probiotic characteristics of *Lactobacillus* strains isolated from cheese and their antibacterial properties against gastrointestinal tract pathogens, Saudi J. Biol. Sci. 27 (2020) 3505-3513. http://doi.org/10.1016/j.sjbs.2020.10.022.

[17] C. Callewaert, N. Knödlseder, A. Karoglan, et al., Skin microbiome transplantation and manipulation: current state of the art, Comput. Struct. Biotechnol. J. 19 (2021) 624-631. http://doi.org/10.1016/j.csbj.2021.01.001.

[18] H.J. Jang, J.H. Kim, N.K. Lee, et al., Inhibitory effects of *Lactobacillus brevis* KU15153 against *Streptococcus mutans* KCTC 5316 causing dental caries, Microb. Pathog. 157 (2021) 104938. http://doi.org/10.1016/j.micpath.2021.104938.

[19] S.K. Han, Y.J. Shin, D.Y. Lee, et al., *Lactobacillus rhamnosus* HDB1258 modulates gut microbiota-mediated immune response in mice with or without lipopolysaccharide-induced systemic inflammation, BMC Microbiol. 21 (2021) 1-15. http://doi.org/10.1186/s12866-021-02192-4.

[20] P. Chandrashekhar, F. Minooei, W. Arreguin, et al., Perspectives on existing and novel alternative intravaginal probiotic delivery methods in the context of bacterial vaginosis infection, AAPS J. 23 (2021) 1-16. http://doi.org/10.1208/s12248-021-00602-z.

[21] S. Ahadian, J.A. Finbloom, M. Mofidfar, et al., Micro and nanoscale technologies in oral drug delivery, Adv. Drug Delivery Rev. 157 (2020) 37-62. http://doi.org/10.1016/j.addr.2020.07.012.

[22] S. Li, A. Xie, H. Li, et al., A self-assembled, ROS-responsive Janus-prodrug for targeted therapy of inflammatory bowel disease, J. Control. Release 316 (2019) 66-78. http://doi.org/10.1016/j.jconrel.2019.10.054.

[23] T. Zhang, J. Jiang, J. Liu, et al., MK2 is required for neutrophil-derived ROS production and inflammatory bowel disease, Front. Med. 7 (2020) 207. http://doi.org/10.3389/fmed.2020.00207.

[24] C.J. Kiely, P. Pavli, C.L. O'Brien, The microbiome of translocated bacterial populations in patients with and without inflammatory bowel disease, Intern. Med. J. 48 (2018) 1346-1354. http://doi.org/10.1111/imj.13998.

[25] M.M. Luchetti, F. Ciccia, C. Avellini, et al., Gut epithelial impairment, microbial translocation and immune system activation in inflammatory bowel disease-associated spondyloarthritis, Rheumatology 60 (2021) 92-102. http://doi.org/10.1093/rheumatology/keaa164.

[26] N. Tajik, M. Frech, O. Schulz, et al., Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis, Nat. Commun. 11 (2020) 1-14. http://doi.org/10.1038/s41467-020-15831-7.

[27] H. Wang, W. Zhang, L. Zuo, et al., Intestinal dysbacteriosis contributes to decreased intestinal mucosal barrier function and increased bacterial

translocation, Lett. Appl. Microbiol. 58 (2014) 384-392. http://doi.org/10.1111/lam.12201.

[28] F. Centurion, A.W. Basit, J. Liu, et al., Nanoencapsulation for probiotic delivery, ACS Nano 15 (2021) 18653-18660. http://doi.org/10.1021/acsnano.1c09951.

[29] C. Xu, Q. Ban, W. Wang, et al., Novel nano-encapsulated probiotic agents: encapsulate materials, delivery, and encapsulation systems, J. Control. Release 349 (2022) 184-205. http://doi.org/10.1016/j.jconrel.2022.06.061.

[30] A.J. Garcia-Brand, V. Quezada, C. Gonzalez-Melo, et al., Novel developments on stimuli-responsive probiotic encapsulates: from smart hydrogels to nanostructured platforms, Fermentation 8 (2022) 117. http://doi.org/10.3390/fermentation8030117.

[31] M.S. Abbas, F. Saeed, M. Afzaal, et al., Recent trends in encapsulation of probiotics in dairy and beverage: a review, J. Food Process. Preserv. 46 (2022) e16689. http://doi.org/10.1111/jfpp.16689.

[32] S. Razavi, S. Janfaza, N. Tasnim, et al., Nanomaterial-based encapsulation for controlled gastrointestinal delivery of viable probiotic bacteria, Nanoscale Adv. 3 (2021) 2699-2709. http://doi.org/10.1039/D0NA00952K.

[33] K. Yoha, S. Nida, S. Dutta, et al., Targeted delivery of probiotics: perspectives on research and commercialization, Probiotics Antimicrob. Proteins (2021) 1-34. http://doi.org/10.1007/s12602-021-09791-7.

[34] Z. Cao, X. Wang, Y. Pang, et al., Biointerfacial self-assembly generates lipid membrane coated bacteria for enhanced oral delivery and treatment, Nat. Commun. 10 (2019) 1-11. http://doi.org/10.1038/s41467-019-13727-9.

[35] J.A. Silva, P.R. De Gregorio, G. Rivero, et al., Immobilization of vaginal *Lactobacillus* in polymeric nanofibers for its incorporation in vaginal probiotic products, Eur. J. Pharm. Sci. 156 (2021) 105563. http://doi.org/10.1016/j.ejps.2020.105563.

[36] C. Pan, J. Li, W. Hou, et al., Polymerization-mediated multifunctionalization of living cells for enhanced cell-based therapy, Adv. Mater. 33 (2021) 2007379. http://doi.org/10.1002/adma.202007379.

[37] S.F. Hosseini, B. Ansari, A. Gharsallaoui, Polyelectrolytes-stabilized liposomes for efficient encapsulation of *Lactobacillus rhamnosus* and improvement of its survivability under adverse conditions, Food Chem. 372 (2022) 131358. http://doi.org/10.1016/j.foodchem.2021.131358.

[38] F. Ghibaudo, E. Gerbino, G.J. Copello, et al., Pectin-decorated magnetite nanoparticles as both iron delivery systems and protective matrices for probiotic bacteria, Colloids Surf. B 180 (2019) 193-201. http://doi.org/10.1016/j.colsurfb.2019.04.049.

[39] F. Islam, M. Noman, M. Afzaal, et al., Synthesis and food applications of resistant starch-based nanoparticles, J. Nanomater. 2022 (2022) 8729258. http://doi.org/10.1155/2022/8729258.

[40] F. Centurion, S. Merhebi, M. Baharfar, et al., Cell-mediated biointerfacial phenolic assembly for probiotic nano encapsulation, Adv. Funct. Mater. (2022) 2200775. http://doi.org/10.1002/adfm.202200775.

[41] J. Pan, G. Gong, Q. Wang, et al., A single-cell nanocoating of probiotics for enhanced amelioration of antibiotic-associated diarrhea, Nat. Commun. 13 (2022) 1-11. http://doi.org/10.1038/s41467-022-29672-z.

[42] W.F. Song, W.Q. Yao, Q.W. Chen, et al., *In situ* bioorthogonal conjugation of delivered bacteria with gut inhabitants for enhancing probiotics colonization, ACS Cent. Sci. 8 (2022) 1306-1317. http://doi.org/10.1021/acscentsci.2c00533.

[43] A.M. Vargason, S. Santhosh, A.C. Anselmo, Surface modifications for improved delivery and function of therapeutic bacteria, Small 16 (2020) 2001705. http://doi.org/10.1002/smll.202001705.

[44] S. Raghuwanshi, R. Agarwal, R. Raval, et al., Chitosan nanoparticles and their applications in drug delivery, hemostasis, and stem cell research, in D. Thangadurai, J. Sangeetha, R. Prasad (Eds.), Functional bionanomaterials from biomolecules to nanoparticles, Spinger, 2020, pp. 129-143. http://doi.org/10.1007/978-3-030-41464-1_6.

[45] F. Pati, B. Adhikari, S. Dhara, Development of chitosan-tripolyphosphate fibers through pH dependent ionotropic gelation, Carbohydr. Res. 346 (2011) 2582-2588. http://doi.org/10.1016/j.carres.2011.08.028.

[46] W. Liu, X.L. Yang, W.W. Ho, Preparation of uniform-sized multiple emulsions and micro/nano particulates for drug delivery by membrane emulsification, J. Pharm. Sci. 100 (2011) 75-93. http://doi.org/10.1002/jps.22272.

[47] Y.S. Leong, F. Candau, Inverse microemulsion polymerization, J. Phys. Chem. 86 (1982) 2269-2271. http://doi.org/10.1021/j100210a001.

[48] S. Chen, Y. Cao, L.R. Ferguson, et al., Evaluation of mucoadhesive coatings of chitosan and thiolated chitosan for the colonic delivery of microencapsulated probiotic bacteria, J. Microencapsul. 30 (2013) 103-115. http://doi.org/10.3109/02652048.2012.700959.

[49] M.A. Mohammed, J.T. Syeda, K.M. Wasan, et al., An overview of chitosan nanoparticles and its application in non-parenteral drug delivery, Pharmaceutics 9 (2017) 53. http://doi.org/10.3390/pharmaceutics9040053.

[50] N.A. Peppas, Y. Huang, Nanoscale technology of mucoadhesive interactions, Adv. Drug Delivery Rev. 56 (2004) 1675-1687. http://doi.org/10.1016/j.addr.2004.03.001.

[51] K.A. Janes, M.P. Fresneau, A. Marazuela, et al., Chitosan nanoparticles as delivery systems for doxorubicin, J. Control. Release 73 (2001) 255-267. http://doi.org/10.1016/S0168-3659(01)00294-2.

[52] B. Shi, Z. Shen, H. Zhang, et al., Exploring *N*-imidazolyl-*O*-carboxymethyl chitosan for high performance gene delivery, Biomacromolecules 13 (2012) 146-153. http://doi.org/10.1021/bm201380e.

[53] A. Mawad, Y.A. Helmy, A.G. Shalkami, et al., *E. coli* Nissle microencapsulation in alginate-chitosan nanoparticles and its effect on *Campylobacter jejuni in vitro*, Appl. Microbiol. Biotechnol. 102 (2018) 10675-10690. http://doi.org/10.1007/s00253-018-9417-3.

[54] X. Zhou, Q. Guo, M. Guo, et al., Nanoarmour-shielded single-cell factory for bacteriotherapy of Parkinson's disease, J. Control. Release 338 (2021) 742-753. http://doi.org/10.1016/j.jconrel.2021.09.009.

[55] H. Zhao, Y. Du, L. Liu, et al., Oral nanozyme-engineered probiotics for the treatment of ulcerative colitis, J. Mater. Chem. B 10 (2022) 4002-4011. http://doi.org/10.1039/D2TB00300G.

[56] S. Stojanov, A. Berlec, Electrospun nanofibers as carriers of microorganisms, stem cells, proteins, and nucleic acids in therapeutic and other applications, Front. Bioengi. Biotech 8 (2020) 130. http://doi.org/10.3389/fbioe.2020.00130.

[57] Z.M. Huang, Y.Z. Zhang, M. Kotaki, et al., A review on polymer nanofibers by electrospinning and their applications in nanocomposites, Compos. Sci. Technol. 63 (2003) 2223-2253. http://doi.org/10.1016/S0266-3538(03)00178-7.

[58] A. López-Rubio, E. Sanchez, Y. Sanz, et al., Encapsulation of living bifidobacteria in ultrathin PVOH electrospun fibers, Biomacromolecules 10 (2009) 2823-2829. http://doi.org/10.1021/bm900660b.

[59] E. Hirsch, E. Pantea, P. Vass, et al., Probiotic bacteria stabilized in orally dissolving nanofibers prepared by high-speed electrospinning, Food Bioprod. Process. 128 (2021) 84-94. http://doi.org/10.1016/j.fbp.2021.04.016.

[60] J.M.D. Soares, R.E.F. Abreu, M.M.d. Costa, et al., Investigation of *Lactobacillus paracasei* encapsulation in electrospun fibers of Eudragit® L100, Polímeros 30 (2020) e2020025. http://doi.org/10.1590/0104-1428.03020.

[61] F. Fareed, F. Saeed, M. Afzaal, et al., Fabrication of electrospun gum Arabic–polyvinyl alcohol blend nanofibers for improved viability of the probiotic, J. Food Sci. Technol. 59 (2022) 4812-4821. http://doi.org/10.1007/s13197-022-05567-1.

[62] F. Ajalloueian, P.R. Guerra, M.I. Bahl, et al., Multi-layer PLGA-pullulan-PLGA electrospun nanofibers for probiotic delivery, Food Hydrocoll. 123 (2022) 107112. http://doi.org/10.1016/j.foodhyd.2021.107112.

[63] J. Wang, K. Liu, R. Xing, et al., Peptide self-assembly: thermodynamics and kinetics, Chem. Soc. Rev. 45 (2016) 5589-5604. http://doi.org/10.1039/C6CS00176A.

[64] J. Yang, M.A.C. Stuart, M. Kamperman, Jack of all trades: versatile catechol crosslinking mechanisms, Chem. Soc. Rev. 43 (2014) 8271-8298. http://doi.org/10.1039/C4CS00185K.

[65] W. Hou, J. Li, Z. Cao, et al., Decorating bacteria with a therapeutic nanocoating for synergistically enhanced biotherapy, Small 17 (2021) 2101810. http://doi.org/10.1002/smll.202101810.

[66] D. Payra, M. Naito, Y. Fujii, et al., Hydrophobized plant polyphenols: self-assembly and promising antibacterial, adhesive, and anticorrosion coatings, Chem. Commun. 52 (2016) 312-315. http://doi.org/10.1039/C5CC07090B.

[67] G. Fan, P. Wasuwanich, M.R. Rodriguez-Otero, et al., Protection of anaerobic microbes from processing stressors using metal-phenolic networks, J. Am. Chem. Soc. 144 (2021) 2438-2443. http://doi.org/10.1021/jacs.1c09018.

[68] J. Liu, W. Li, Y. Wang, et al., Biomaterials coating for on-demand bacteria delivery: selective release, adhesion, and detachment, Nano Today 41 (2021) 101291. http://doi.org/10.1016/j.nantod.2021.101291.

[69] M. Tallawi, M. Opitz, O. Lieleg, Modulation of the mechanical properties of bacterial biofilms in response to environmental challenges, Biomater. Sci. 5 (2017) 887-900. http://doi.org/10.1039/C6BM00832A.

[70] B. Mielich-Süss, D. Lopez, Molecular mechanisms involved in *Bacillus subtilis* biofilm formation, Environ. Microbiol. 17 (2015) 555-565. http://doi.org/10.1111/1462-2920.12527.

[71] M. Simões, L.C. Simões, M.J. Vieira, A review of current and emergent biofilm control strategies, LWT-Food Sci. Tech. 43 (2010) 573-583. http://doi.org/10.1016/j.lwt.2009.12.008.

[72] X. Wang, Z. Cao, M. Zhang, et al., Bioinspired oral delivery of gut microbiota by self-coating with biofilms, Sci. Adv. 6 (2020) eabb1952. http://doi.org/10.1126/sciadv.abb1952.

[73] S. Yahav, Z. Berkovich, I. Ostrov, et al., Encapsulation of beneficial probiotic bacteria in extracellular matrix from biofilm-forming *Bacillus subtilis*, Artif. Cells Nanomed. Biotechnol. 46 (2018) 974-982. http://doi.org/10.1080/21691401.2018.1476373.

[74] Z. Li, A.M. Behrens, N. Ginat, et al., Biofilm-inspired encapsulation of probiotics for the treatment of complex infections, Adv. Mater. 30 (2018) 1803925. http://doi.org/10.1002/adma.201803925.

[75] C. Yucel Falco, F. Amadei, S.K. Dhayal, et al., Hybrid coating of alginate microbeads based on protein-biopolymer multilayers for encapsulation of probiotics, Biotechnol. Prog. 35 (2019) e2806. http://doi.org/10.1002/btpr.2806.

[76] T. Tolker-Nielsen, Biofilm development, Microbiol. Spectrum. 3 (2015) MB-0001-2014. http://doi.org/10.1128/microbiolspec.MB-0001-2014.

[77] Q. Song, H. Zhao, C. Zheng, et al., A bioinspired versatile spore coat nanomaterial for oral probiotics delivery, Adv. Funct. Mater. 31 (2021) 2104994. http://doi.org/10.1002/adfm.202104994.

[78] H. Ejima, J.J. Richardson, K. Liang, et al., One-step assembly of coordination complexes for versatile film and particle engineering, Science 341 (2013) 154-157. http://doi.org/10.1126/science.1237265.

[79] X. Yang, J. Yang, Z. Ye, et al., Physiologically inspired mucin coated *Escherichia coli* Nissle 1917 enhances biotherapy by regulating the pathological microenvironment to improve intestinal colonization, ACS Nano 16 (2022) 4041-4058. http://doi.org/10.1021/acsnano.1c09681.

[80] J. Yang, G. Zhang, X. Yang, et al., An oral "super probiotics" with versatile self-assembly adventitia for enhanced intestinal colonization by autonomous regulating the pathological microenvironment, Chem. Eng. J. (2022) 137204. http://doi.org/10.1016/j.cej.2022.137204.

[81] X. Wang, S. Gao, S. Yun, et al., Microencapsulating alginate-based polymers for probiotics delivery systems and their application, Pharmaceuticals 15 (2022) 644. http://doi.org/10.3390/ph15050644.

[82] I.A. Sogias, A.C. Williams, V.V. Khutoryanskiy, Why is chitosan mucoadhesive? Biomacromolecules 9 (2008) 1837-1842. http://doi.org/10.1021/bm800276d.

[83] D. Chickering, E. Mathiowitz, Bioadhesive microspheres: I. A novel electrobalance-based method to study adhesive interactions between individual microspheres and intestinal mucosa, J. Control. Release 34 (1995) 251-262. http://doi.org/10.1016/0168-3659(95)00011-V.

[84] A.C. Anselmo, K.J. McHugh, J. Webster, et al., Layer-by-layer encapsulation of probiotics for delivery to the microbiome, Adv. Mater. 28 (2016) 9486-9490. http://doi.org/10.1002/adma.201603270.

[85] P. Ambalam, J. Dave, B.M. Nair, et al., *In vitro* mutagen binding and antimutagenic activity of human *Lactobacillus rhamnosus* 231, Anaerobe 17 (2011) 217-222. http://doi.org/10.1016/j.anaerobe.2011.07.001.

[86] D. Gorman-Lewis, W. Martens-Habbena, D. Stahl, Thermodynamic characterization of proton-ionizable functional groups on the cell surfaces of ammonia-oxidizing bacteria and archaea, Geobiol. 12 (2014) 157-171. http://doi.org/10.1111/gbi.12075.

[87] D. Michelon, S. Abraham, B. Ebel, et al., Contribution of exofacial thiol groups in the reducing activity of *Lactococcus lactis*, FEBS J. 277 (2010) 2282-2290. http://doi.org/10.1111/j.1742-4658.2010.07644.x.

[88] A. Bernkop-Schnürch, A.H. Krauland, V.M. Leitner, et al., Thiomers: potential excipients for non-invasive peptide delivery systems, Eur. J. Pharm. Biopharm. 58 (2004) 253-263. http://doi.org/10.1016/j.ejpb.2004.03.032.

[89] V.M. Leitner, G.F. Walker, A. Bernkop-Schnürch, Thiolated polymers: evidence for the formation of disulphide bonds with mucus glycoproteins, Eur. J. Pharm. Biopharm. 56 (2003) 207-214. http://doi.org/10.1016/S0939-6411(03)00061-4.

[90] A. Bernkop-Schnürch, M. Hornof, D. Guggi, Thiolated chitosans, Eur. J. Pharm. Biopharm. 57 (2004) 9-17. http://doi.org/10.1016/S0939-6411(03)00147-4.

[91] Y. Liu, B. Liu, D. Li, et al., Improved gastric acid resistance and adhesive colonization of probiotics by mucoadhesive and intestinal targeted konjac glucomannan microspheres, Adv. Funct. Mater. 30 (2020) 2001157. http://doi.org/10.1002/adfm.202001157.

[92] L. Yang, J.O. Nyalwidhe, S. Guo, et al., Targeted identification of metastasis-associated cell-surface sialoglycoproteins in prostate cancer, Mol. Cell. Proteomics 10 (2011). http://doi.org/10.1074/mcp.M110.007294.

[93] N.K. Surana, D.L. Kasper, The yin yang of bacterial polysaccharides: lessons learned from B. fragilis PSA, Immunol. Rev. 245 (2012) 13-26. http://doi.org/10.1111/j.1600-065X.2011.01075.x.

[94] E. Kuru, H.V. Hughes, P.J. Brown, et al., *In situ* probing of newly synthesized peptidoglycan in live bacteria with fluorescent D-amino acids, Angew. Chem. 124 (2012) 12687-12691. http://doi.org/10.1002/ange.201206749.

[95] L. Lin, J. Song, J. Li, et al., Imaging the *in vivo* growth patterns of bacteria in human gut microbiota, Gut Microbes 13 (2021) 1960134. http://doi.org/10.1080/19490976.2021.1960134.

[96] L. Lin, Q. Wu, J. Song, et al., Revealing the *in vivo* growth and division patterns of mouse gut bacteria, Sci. Adv. 6 (2020) eabb2531. http://doi.org/10.1126/sciadv.abb2531.

[97] W. Wang, L. Lin, Y. Du, et al., Assessing the viability of transplanted gut microbiota by sequential tagging with D-amino acid-based metabolic probes, Nat. Commun. 10 (2019) 1317. http://doi.org/10.1038/s41467-019-09267-x.

[98] E. Kuru, C. Lambert, J. Rittichier, et al., Fluorescent D-amino-acids reveal bi-cellular cell wall modifications important for *Bdellovibrio bacteriovorus* predation, Nat. Microbiol. 2 (2017) 1648-1657. http://doi.org/10.1038/s41564-017-0029-y.

[99] H. Lam, D.C. Oh, F. Cava, et al., D-amino acids govern stationary phase cell wall remodeling in bacteria, Science 325 (2009) 1552-1555. http://doi.org/10.1126/science.1178123.

[100] H.P. Lesch, M.U. Kaikkonen, J.T. Pikkarainen, et al., Avidin-biotin technology in targeted therapy, Expert Opin. Drug Deliv. 7 (2010) 551-564. http://doi.org/10.1517/17425241003677749.

[101] H.C. Flemming, J. Wingender, U. Szewzyk, et al., Biofilms: an emergent form of bacterial life, Nat. Rev. Microbiol. 14 (2016) 563-575. http://doi.org/10.1038/nrmicro.2016.94.

[102] J. Yan, B.L. Bassler, Surviving as a community: antibiotic tolerance and persistence in bacterial biofilms, Cell Host Microbe 26 (2019) 15-21. http://doi.org/10.1016/j.chom.2019.06.002.

[103] S. Lin, S. Mukherjee, J. Li, et al., Mucosal immunity–mediated modulation of the gut microbiome by oral delivery of probiotics into Peyer's patches, Sci. Adv. 7 (2021) eabf0677. http://doi.org/10.1126/sciadv.abf0677.

[104] P. Kaur, S. Ghosh, A. Bhowmick, et al., Bacterioboat—a novel tool to increase the half-life period of the orally administered drug, Sci. Adv. 8 (2022) eabh1419. http://doi.org/10.1126/sciadv.abh1419.

[105] Y.J. Zhu, F. Chen, pH-responsive drug-delivery systems, Chem. Asian J. 10 (2015) 284-305. http://doi.org/10.1002/asia.201402715.

[106] M.T. Cook, G. Tzortzis, V.V. Khutoryanskiy, et al., Layer-by-layer coating of alginate matrices with chitosan-alginate for the improved survival and targeted delivery of probiotic bacteria after oral administration, J. Mater. Chem. B 1 (2013) 52-60. http://doi.org/10.1039/C2TB00126H.

[107] R. Ghaffarian, E. Pérez-Herrero, H. Oh, et al., Chitosan-alginate microcapsules provide gastric protection and intestinal release of ICAM-1-targeting nanocarriers, enabling GI targeting *in vivo*, Adv. Funct. Mater. 26 (2016) 3382-3393. http://doi.org/10.1002/adfm.201600084.

[108] L. Mei, F. He, R.Q. Zhou, et al., Novel intestinal-targeted Ca-alginate-based carrier for pH-responsive protection and release of lactic acid bacteria, ACS Appl. Mater. Interfaces 6 (2014) 5962-5970. http://doi.org/10.1021/am501011j.

[109] M.D.A. Etchepare, J.S. Barin, A.J. Cichoski, et al., Microencapsulation of probiotics using sodium alginate, Cienc. Rural 45 (2015) 1319-1326. http://doi.org/10.1590/0103-8478cr20140938.

[110] W.R. Gombotz, S. Wee, Protein release from alginate matrices, Adv. Drug Delivery Rev. 31 (1998) 267-285. http://doi.org/10.1016/S0169-409X(97)00124-5.

[111] S. Nualkaekul, D. Lenton, M.T. Cook, et al., Chitosan coated alginate beads for the survival of microencapsulated *Lactobacillus plantarum* in pomegranate juice, Carbohydr. Polym. 90 (2012) 1281-1287. http://doi.org/10.1016/j.carbpol.2012.06.073.

[112] S. Mandal, A. Puniya, K. Singh, Effect of alginate concentrations on survival of microencapsulated *Lactobacillus casei* NCDC-298, Int. Dairy J. 16 (2006) 1190-1195. http://doi.org/10.1016/j.idairyj.2005.10.005.

[113] A. El-Salam, H. Mohamed, S. El-Shibiny, Preparation and properties of milk proteins-based encapsulated probiotics: a review, Dairy Sci. Technol. 95 (2015) 393-412. http://doi.org/10.1007/s13594-015-0223-8.

[114] S.S. Dehkordi, I. Alemzadeh, A.S. Vaziri, et al., Optimization of alginate-whey protein isolate microcapsules for survivability and release behavior of probiotic bacteria, Appl. Biochem. Biotechnol. 190 (2020) 182-196. http://doi.org/10.1007/s12010-019-03071-5.

[115] H. Englyst, S. Hay, G. Macfarlane, Polysaccharide breakdown by mixed populations of human faecal bacteria, FEMS Microbiol. Ecol. 3 (1987) 163-171. http://doi.org/10.1111/j.1574-6968.1987.tb02352.x.

[116] L. Yang, Biorelevant dissolution testing of colon-specific delivery systems activated by colonic microflora, J. Control. Release 125 (2008) 77-86. http://doi.org/10.1016/j.jconrel.2007.10.026.

[117] T. Sonia, C.P. Sharma, Chitosan and its derivatives for drug delivery perspective, in R. Jayakumar, M. Prabaharan, R.A.A. Muzzarelli (Eds.), Chitosan for biomaterials I, Springer, 2011, pp. 23-53. http://doi.org/10.1007/12_2011_117.

[118] H.M. El-Husseiny, E.A. Mady, L. Hamabe, et al., Smart/stimuli-responsive hydrogels: Cutting-edge platforms for tissue engineering and other biomedical applications, Mater. Today Bio 13 (2022) 100186. http://doi.org/10.1016/j.mtbio.2021.100186.

[119] I. Kwiecień, M. Kwiecień, Application of polysaccharide-based hydrogels as probiotic delivery systems, Gels 4 (2018) 47. http://doi.org/10.3390/gels4020047.

[120] A. Bepeyeva, J.M. de Barros, H. Albadran, et al., Encapsulation of *Lactobacillus casei* into calcium pectinate-chitosan beads for enteric delivery, J. Food Sci. 82 (2017) 2954-2959. http://doi.org/10.1111/1750-3841.13974.

[121] P. Nangia-Makker, V. Hogan, Y. Honjo, et al., Inhibition of human cancer cell growth and metastasis in nude mice by oral intake of modified citrus pectin, J. Natl. Cancer Inst. 94 (2002) 1854-1862. http://doi.org/10.1093/jnci/94.24.1854.

[122] J. Zhu, L. Zhong, W. Chen, et al., Preparation and characterization of pectin/chitosan beads containing porous starch embedded with doxorubicin hydrochloride: a novel and simple colon targeted drug delivery system, Food Hydrocoll. 95 (2019) 562-570. http://doi.org/10.1016/j.foodhyd.2018.04.042.

[123] S.A. Zawko, C.E. Schmidt, Crystal templating dendritic pore networks and fibrillar microstructure into hydrogels, Acta Biomater. 6 (2010) 2415-2421. http://doi.org/10.1016/j.actbio.2010.02.021.

[124] Y. Zhang, L. Dong, L. Liu, et al., Recent advances of stimuli-responsive polysaccharide hydrogels in delivery systems: a review, J. Agric. Food Chem. 70 (2022) 6300-6316. http://doi.org/10.1021/acs.jafc.2c01080.

[125] Y. Xiao, C. Lu, Y. Liu, et al., Encapsulation of *Lactobacillus rhamnosus* in hyaluronic acid-based hydrogel for pathogen-targeted delivery to ameliorate enteritis, ACS Appl. Mater. Interfaces 12 (2020) 36967-36977. http://doi.org/10.1021/acsami.0c11959.

[126] C. Vanderpool, F. Yan, B.D. Polk, Mechanisms of probiotic action: implications for therapeutic applications in inflammatory bowel diseases, Inflamm. Bowel Dis. 14 (2008) 1585-1596. http://doi.org/10.1002/ibd.20525.

[127] J. Wang, H. Ji, S. Wang, et al., Probiotic *Lactobacillus plantarum* promotes intestinal barrier function by strengthening the epithelium and modulating gut microbiota, Front. Microbiol. 9 (2018) 1953. http://doi.org/10.3389/fmicb.2018.01953.

[128] R. di Vito, C. Conte, G. Traina, A multi-strain probiotic formulation improves intestinal barrier function by the modulation of tight and adherent junction proteins, Cells 11 (2022) 2617. http://doi.org/10.3390/cells11162617.

[129] L. Wang, H. Cao, L. Liu, et al., Activation of epidermal growth factor receptor mediates mucin production stimulated by p40, a *Lactobacillus rhamnosus* GG-derived protein, J. Biol. Chem. 289 (2014) 20234-20244. http://doi.org/10.1074/jbc.M114.553800.

[130] Y. Tobisawa, Y. Imai, M. Fukuda, et al., Sulfation of colonic mucins by *N*-acetylglucosamine 6-*O*-sulfotransferase-2 and its protective function in experimental colitis in mice, J. Biol. Chem. 285 (2010) 6750-6760. http://doi.org/10.1074/jbc.M109.067082.

[131] M. Schultz, Clinical use of *E. coli* Nissle 1917 in inflammatory bowel disease, Inflamm. Bowel Dis. 14 (2008) 1012-1018. http://doi.org/10.1002/ibd.20377.

[132] M. Schlee, J. Wehkamp, A. Altenhoefer, et al., Induction of human β-defensin 2 by the probiotic *Escherichia coli* Nissle 1917 is mediated through flagellin, Infect. Immun. 75 (2007) 2399-2407. http://doi.org/10.1128/IAI.01563-06.

[133] L. Mandel, I. Trebichavsky, I. Splichal, et al., Stimulation of intestinal immune cells by E. coli in gnotobiotic piglets, Adv. Mucosal Immunol. 371 (1995) 463-464. http://doi.org/10.1007/978-1-4615-1941-6_96.

[134] A. Altenhoefer, S. Oswald, U. Sonnenborn, et al., The probiotic *Escherichia coli* strain Nissle 1917 interferes with invasion of human intestinal epithelial cells by different enteroinvasive bacterial pathogens, FEMS Immunol. Med. Microbiol. 40 (2004) 223-229. http://doi.org/10.1016/S0928-8244(03)00368-7.

[135] J. Boudeau, A.L. Glasser, S. Julien, et al., Inhibitory effect of probiotic *Escherichia coli* strain Nissle 1917 on adhesion to and invasion of intestinal epithelial cells by adherent-invasive *E. coli* strains isolated from patients with Crohn's disease, Aliment. Pharmacol. Ther. 18 (2003) 45-56. http://doi.org/10.1046/j.1365-2036.2003.01638.x.

[136] A.C. Ouwehand, S.J. Salminen, The health effects of cultured milk products with viable and non-viable bacteria, Int. Dairy J. 8 (1998) 749-758. http://doi.org/10.1016/S0958-6946(98)00114-9.

[137] G. Young, R. Krasner, P. Yudkofsky, Interactions of oral strains of *Candida albicans* and *Lactobacilli*, J. Bacteriol. 72 (1956) 525-529. http://doi.org/journals.asm.org/journal/jb.

[138] P. Midolo, J. Lambert, R. Hull, et al., *In vitro* inhibition of *Helicobacter pylori* NCTC 11637 by organic acids and lactic acid bacteria, J. Appl. Bacteriol. 79 (1995) 475-479. http://doi.org/10.1111/j.1365-2672.1995.tb03164.x.

[139] C.M. Slover, L. Danziger, *Lactobacillus*: a review, Clin. Microbiol. Newsl. 30 (2008) 23-27. http://doi.org/10.1016/j.clinmicnews.2008.01.006.

[140] D. Bujnakova, E. Strakova, V. Kmet, *In vitro* evaluation of the safety and probiotic properties of *Lactobacilli* isolated from chicken and calves, Anaerobe 29 (2014) 118-27. http://doi.org/10.1016/j.anaerobe.2013.10.009.

[141] C. Sharma, B.P. Singh, N. Thakur, et al., Antibacterial effects of *Lactobacillus* isolates of curd and human milk origin against food-borne and human pathogens, 3 Biotech 7 (2017) 1-9. http://doi.org/10.1007/s13205-016-0591-7.

[142] M. Candela, F. Perna, P. Carnevali, et al., Interaction of probiotic *Lactobacillus* and *Bifidobacterium* strains with human intestinal epithelial cells: adhesion properties, competition against enteropathogens and modulation of IL-8 production, Int. J. Food Microbiol. 125 (2008) 286-292. http://doi.org/10.1016/j.ijfoodmicro.2008.04.012.

[143] P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, Nat. Rev. Immunol. 11 (2011) 723-737. http://doi.org/10.1038/nri3073.

[144] L. Guo, M. Meng, Y. Wei, et al., Protective effects of live combined *B. subtilis* and *E. faecium* in polymicrobial sepsis through modulating activation and transformation of macrophages and mast cells, Front. Pharmacol. 9 (2019) 1506. http://doi.org/10.3389/fphar.2018.01506.

[145] C. Hee Kim, H. Geun Kim, J. Yun Kim, et al., Probiotic genomic DNA reduces the production of pro-inflammatory cytokine tumor necrosis factor-alpha, FEMS Microbiol. Lett. 328 (2012) 13-19. http://doi.org/10.1111/j.1574-6968.2011.02470.x.

[146] G. Leccese, A. Bibi, S. Mazza, et al., Probiotic *Lactobacillus* and *Bifidobacterium* strains counteract adherent-invasive *Escherichia coli* (AIEC) virulence and hamper IL-23/Th17 axis in ulcerative colitis, but not in crohn's disease, Cells 9 (2020) 1824. http://doi.org/10.3390/cells9081824.

[147] Y. Nishitani, T. Tanoue, K. Yamada, et al., *Lactococcus lactis* subsp. cremoris FC alleviates symptoms of colitis induced by dextran sulfate sodium in mice, Int. Immunopharmacol. 9 (2009) 1444-1451. http://doi.org/10.1016/j.intimp.2009.08.018.

[148] M. Liu, X. Zhang, Y. Hao, et al., Protective effects of a novel probiotic strain, *Lactococcus lactis* ML2018, in colitis: *in vivo* and *in vitro* evidence, Food Funct. 10 (2019) 1132-1145. http://doi.org/10.1039/C8FO02301H.

[149] M. Ghebretatios, S. Schaly, S. Prakash, Nanoparticles in the food industry and their impact on human gut microbiome and diseases, Int. J. Mol. Sci. 22 (2021) 1942. http://doi.org/10.3390/ijms22041942.

[150] D.J. McClements, H. Xiao, Is nano safe in foods? Establishing the factors impacting the gastrointestinal fate and toxicity of organic and inorganic food-grade nanoparticles, npj Sci. Food 1 (2017) 1-13. http://doi.org/10.1038/s41538-017-0005-1.

[151] A.d.l.C. Pech-Canul, D. Ortega, A. García-Triana, et al., A brief review of edible coating materials for the microencapsulation of probiotics, Coatings 10 (2020) 197. http://doi.org/10.3390/coatings10030197.

[152] L. Liu, W. Yao, Y. Rao, et al., pH-Responsive carriers for oral drug delivery: challenges and opportunities of current platforms, Drug Delivery 24 (2017) 569-581. http://doi.org/10.1080/10717544.2017.1279238.

[153] G. Christie, P. Setlow, *Bacillus* spore germination: knowns, unknowns and what we need to learn, Cell. Signal. 74 (2020) 109729. http://doi.org/10.1016/j.cellsig.2020.109729.

[154] I.L. Wu, K. Narayan, J.-P. Castaing, et al., A versatile nano display platform from bacterial spore coat proteins, Nat. Commun. 6 (2015) 1-8. http://doi.org/10.1038/ncomms7777(2015).

[155] N. Viratchaiboott, P. Sakunpongpitiporn, S. Niamlang, et al., Release of 5-FU loaded pectin/Fe_3O_4 from porous PBSA matrix under magnetic and electric fields, J. Alloys Compd. 906 (2022) 164239. http://doi.org/10.1016/j.jallcom.2022.164239.

[156] W. Wang, X. Qiao, J. Chen, The role of acetic acid in magnesium oxide preparation via chemical precipitation, J. Am. Ceram. Soc. 91 (2008) 1697-1699. http://doi.org/10.1111/j.1551-2916.2008.02326.x.

[157] M. Yao, B. Li, H. Ye, et al., Enhanced viability of probiotics (*Pediococcus pentosaceus* Li05) by encapsulation in microgels doped with inorganic nanoparticles, Food Hydrocoll. 83 (2018) 246-252. http://doi.org/10.1016/j.foodhyd.2018.05.024.

[158] Q. Luan, W. Zhou, H. Zhang, et al., Cellulose-based composite macrogels from cellulose fiber and cellulose nanofiber as intestine delivery vehicles for probiotics, J. Agric. Food Chem. 66 (2018) 339-345. http://doi.org/10.1021/acs.jafc.7b04754.

[159] A. Dafe, H. Etemadi, A. Dilmaghani, et al., Investigation of pectin/starch hydrogel as a carrier for oral delivery of probiotic bacteria, Int. J. Biol. Macromol. 97 (2017) 536-543. http://doi.org/10.1016/j.ijbiomac.2017.01.060.

[160] D. Lin, Y. Ma, W. Qin, et al., The structure, properties and potential probiotic properties of starch-pectin blend: a review, Food Hydrocoll. 129 (2022) 107644. http://doi.org/10.1016/j.foodhyd.2022.107644.

[161] Y. Liu, Y. Sun, L. Sun, et al., *In vitro* and *in vivo* study of sodium polyacrylate grafted alginate as microcapsule matrix for live probiotic delivery, J. Funct. Foods 24 (2016) 429-437. http://doi.org/10.1016/j.jff.2016.03.034.

[162] X. Ding, Y. Xu, Y. Wang, et al., Carboxymethyl konjac glucomannan-chitosan complex nanogels stabilized double emulsions incorporated into alginate hydrogel beads for the encapsulation, protection and delivery of probiotics, Carbohydr. Polym. 289 (2022) 119438. http://doi.org/10.1016/j.carbpol.2022.119438.

[163] X. Qi, S. Simsek, J.B. Ohm, et al., Viability of *Lactobacillus rhamnosus* GG microencapsulated in alginate/chitosan hydrogel particles during storage and simulated gastrointestinal digestion: role of chitosan molecular weight, Soft Matter 16 (2020) 1877-1887. http://doi.org/10.1039/C9SM02387A.

[164] D. Wu, J. Wan, J. Lu, et al., Chitosan coatings on lecithin stabilized emulsions inhibit mycotoxin production by *Fusarium* pathogens, Food Control 92 (2018) 276-285. http://doi.org/10.1016/j.foodcont.2018.05.009.

[165] J. Hirata, N. Kurokawa, M. Okano, et al., Evaluation of crystallinity and hydrogen bond formation in stereocomplex poly (lactic acid) films by terahertz time-domain spectroscopy, Macromolecules 53 (2020) 7171-7177. http://doi.org/10.1021/acs.macromol.0c00237.

[166] H. Yu, W. Liu, D. Li, et al., Targeting delivery system for *Lactobacillus plantarum* based on functionalized electrospun nanofibers, Polymers 12 (2020) 1565. http://doi.org/10.3390/polym12071565.

[167] J. Ma, C. Xu, H. Yu, et al., Electro-encapsulation of probiotics in gum Arabic-pullulan blend nanofibres using electrospinning technology, Food Hydrocoll. 111 (2021) 106381. http://doi.org/10.1016/j.foodhyd.2020.106381.

[168] S.J. Mojaveri, S.F. Hosseini, A. Gharsallaoui, Viability improvement of *Bifidobacterium animalis* Bb12 by encapsulation in chitosan/poly (vinyl alcohol) hybrid electrospun fiber mats, Carbohydr. Polym. 241 (2020) 116278. http://doi.org/10.1016/j.carbpol.2020.116278.

[169] H. Zheng, Y. Du, J. Yu, et al., Preparation and characterization of chitosan/poly (vinyl alcohol) blend fibers, J. Appl. Polym. Sci. 80 (2001) 2558-2565. http://doi.org/10.1002/app.1365.

[170] R. Atraki, M. Azizkhani, Survival of probiotic bacteria nanoencapsulated within biopolymers in a simulated gastrointestinal model, Innovative Food Sci. Emerg. Technol. 72 (2021) 102750. http://doi.org/10.1016/j.ifset.2021.102750.

[171] N. Alavi, M.T. Golmakani, S.M.H. Hosseini, Fabrication and characterization of phycocyanin-alginate-pregelatinized corn starch composite gel beads: effects of carriers on kinetic stability of phycocyanin, Int. J. Biol. Macromol. 218 (2022) 665-678. http://doi.org/10.1016/j.ijbiomac.2022.07.111.

[172] C.Y. Falco, J. Sotres, A. Rascón, et al., Design of a potentially prebiotic and responsive encapsulation material for probiotic bacteria based on chitosan and sulfated β-glucan, J. Colloid Interface Sci. 487 (2017) 97-106. http://doi.org/10.1016/j.jcis.2016.10.019.

[173] F. Wang, J. Li, X. Tang, et al., Polyelectrolyte three layer nanoparticles of chitosan/dextran sulfate/chitosan for dual drug delivery, Colloids Surf. B 190 (2020) 110925. http://doi.org/10.1016/j.colsurfb.2020.110925.

[174] R.J. Mu, Y. Yuan, L. Wang, et al., Microencapsulation of *Lactobacillus acidophilus* with konjac glucomannan hydrogel, Food Hydrocoll. 76 (2018) 42-48. http://doi.org/10.1016/j.foodhyd.2017.07.009.

[175] L.Y. Zheng, J.M. Shi, Y.H. Chi, Tannic acid physically cross-linked responsive hydrogel, Macromol. Chem. Phys. 219 (2018) 1800234. http://doi.org/10.1002/macp.201800234.

[176] P.Y. Liu, Z.H. Miao, K. Li, et al., Biocompatible Fe^{3+}-TA coordination complex with high photothermal conversion efficiency for ablation of cancer cells, Colloids Surf. B 167 (2018) 183-190. http://doi.org/10.1016/j.colsurfb.2018.03.030.

[177] K.L. Meng, X.C. Lv, H.Y. Che, et al., Joint protection strategies for *Saccharomyces boulardii*: exogenous encapsulation and endogenous biofilm structure, Appl. Microbiol. Biotechnol. 105 (2021) 8469-8479. http://doi.org/10.1007/s00253-021-11601-7.