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TARGETED PROBIOTIC DELIVERY VIA BACTERIOPHAGE-RESISTANT CAPSULES: A NOVEL APPROACH TO ENHANCE GUT HEALTH

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Abstract

Probiotics are live microorganisms that have beneficial health effects when taken. Because they may be harmed by gastrointestinal tract disorders, beneficial bacteria must be delivered through effective mechanisms in order to maximize their potential. By using bacteriophage-resistant capsules for targeted probiotic delivery, the study aims to investigate a novel approach to enhancing gut health. The review investigates how combining bacteriophage-resistant capsules with different encapsulation techniques can improve the survivability, specificity, and efficacy of probiotics in the GI tract. The study looks at phage-resistant capsules, complex interactions between phages and probiotics, and various encapsulation methods for bacteriophages and probiotics, including hydrogels, spray drying, liposomes, and microencapsulation. It concludes that by combining advanced encapsulation techniques with bacteriophage-resistant capsules, R-capsule technology can alter microbiota, treat illness, improve nutritional outcomes, extend the shelf life of probiotics, and create customized gut health regimens.

Keywords: *Bacteriophage-resistant capsules, Delivery systems, Encapsulation, Gut health, Microbiota, Probiotics*

INTRODUCTION

Probiotics are live microorganisms that, when taken in suitable quantities, provide health advantages to the host (1, 2). Dysbiosis, which disrupts the human gastrointestinal microbiota, a vital community of microorganisms, is the cause of GI disorders such as IBS, IBD, and antibiotic-associated diarrhea. Probiotics are used to enhance gut health by changing the microbiota and inhibiting harmful bacteria (1).Despite being researched for over a century, the clinical success of probiotics in treating GI disorders varies greatly, affected by factors like the specific microbial strain used, dosage, and the challenging environment of the digestive system (1, 2). Probiotics are sold in numerous formats—including capsules, tablets, powders, and fermented foods—but their ability to survive the journey through the upper GI tract depends significantly on the delivery method (2-4). Therefore, effective and targeted delivery systems are now recognized as essential to fully realizing the health-promoting potential of probiotics.

The R-capsule technology, which combines bacteriophages and state-of-the-art encapsulating techniques, extends the life of probiotics by targeting specific bacterial strains and protecting them from bile salts and stomach acid. This innovative approach makes it possible to tailor microbial modulation to each patient's unique health profile by offering personalized gut health plans (2-4). However, certain obstacles remain. The human safety and effectiveness of phage-based systems are still under active study, and regulatory standards for these advanced therapies are in the process of being defined (3, 5). Phage-R capsules require scalable manufacturing processes for clinical and commercial use; however, phage technology in conjunction with state-of-the-art encapsulation platforms may enhance probiotic efficacy and medical applications.

The therapeutic use of probiotics has gained global recognition due to their beneficial effects on gut microbiota, immunity, and overall health. However, one of the major challenges in probiotic therapy is their susceptibility to bacteriophage attack, which can drastically reduce their viability before reaching the

intestine. Traditional encapsulation methods improve probiotic survival against gastric acidity and bile salts but often fail to protect against phage predation. Recent advancements in microencapsulation technology have led to the development of bacteriophage-resistant capsules designed to enhance the targeted delivery of probiotics to the gastrointestinal tract. These innovative delivery systems not only shield probiotics from phage infection but also ensure their controlled release at the desired intestinal site. This strategy represents a promising approach for maintaining probiotic efficacy in functional foods, nutraceuticals, and clinical applications (5).

METHODOLOGY

DATA COLLECTION

As part of the literature review's data collection process, peer-reviewed articles were methodically located and evaluated. The publications were found using the following keywords: Encapsulation, Gut health, Microbiota, Delivery systems, R-capsule technology, Encapsulation methods, Gastrointestinal (GI) tract.

ARTICLE SELECTION

We selected articles from the PubMed, Scopus, Web of Science, and Google Scholar databases. Depending on their applicability, systemic reviews, clinical trials, meta-analyses, and cohort studies were considered for Bacteriophages as Targeted Therapeutic Vehicles. Only English-language works published in indexed journals between 2015 and 2025 were included in the selection process, with an emphasis on subjects like Targeted delivery of probiotics to enhance gastrointestinal stability and intestinal colonization.

KEY CHALLENGES IN PROBIOTIC DELIVERY

STOMACH ACIDITY DAMAGES PROTEINS AND CELL WALLS

The stomach's highly acidic environment (pH 1.0–3.5) presents a major hurdle for probiotics (2-4). Although essential for digestion and pathogen control, this low pH harms probiotic cells by acidifying their internal environment, denaturing proteins, and damaging cell walls (2-4). Enzymes like pepsin, active in acidic conditions, further degrade bacterial proteins, leading to cell death. Up to 60% of probiotics can be destroyed before reaching the intestine (2). To offset this, high initial doses are often administered, but without protective measures, survival remains low (2-4).

Basic probiotic forms, such as uncoated tablets, provide little protection. Enteric-coated capsules using materials like hydroxypropyl methylcellulose phthalate or carboxymethyl high amylose starch improve survival by dissolving in the more neutral pH of the intestine (2). Still, these are not always effective, especially for more delicate strains. The R-capsule system introduces a smarter solution by releasing probiotics in response to specific gut triggers like pH or enzymes (2-4), especially when combined with phage targeting.

BILE SALTS COMPROMISE CELL MEMBRANES

After passing through the stomach, probiotics encounter bile salts in the small intestine, which act as detergents that disrupt cell membranes and denature proteins, leading to leakage and cell damage (2, 3). Unconjugated bile salts can infiltrate bacterial cells and inflict even greater harm. Some strains possess bile salt hydrolase (BSH) enzymes to detoxify bile salts, but many do not.

The extent of bile salt damage depends on concentration, bile salt type, and the microbial cell membrane's characteristics. Since traditional formulations offer little protection, the viability of probiotics can be significantly reduced (2, 3). R-capsules are designed to guard probiotics until they arrive in the colon, where bile salt concentrations are lower, improving their survival (2-4). Pairing this with phage targeting enhances the overall precision and effectiveness of delivery.

DIGESTIVE ENZYMES BREAK DOWN PROTEINS AND DNA

Digestive enzymes like proteases, lipases, and amylases, present in the small intestine, break down not only food but also probiotics, leading to loss of function and cell lysis (4, 5). This adds to the already harsh conditions created by stomach acid and bile salts.

To combat this, various encapsulation techniques, including alginate, chitosan, and advanced polymers, have been developed (6, 7). These methods increase stability during storage and transit. However, their success depends on the choice of material, encapsulation method, and the trigger used for controlled release in the gut.

By combining bacteriophage targeting with advanced encapsulation systems, such as the R-capsule, probiotics can be more effectively protected and precisely delivered. This synergy marks a significant advancement in probiotic therapy, offering potential improvements in gut health and expanding clinical applications (5, 6).

ENCAPSULATION STRATEGIES FOR PROBIOTICS AND PHAGES

A common therapeutic strategy that offers advantages over free phages is phage encapsulation. Encapsulation aims to produce uniform, non-clumping particles and maintain a constant quantity of phages in each particle to guarantee precise dosage and fulfill a range of purposes. The provided figure no 1 illustrate that three different strategies for delivering bacteriophages, supporting the encapsulation concepts discussed in the text.

- Defense: Encapsulation, such as with liposomes, protects the payload against immune system components' inactivation, hydrolysis (at low pH), and enzymatic destruction.
- Consistency: Since phages are biological beings, they lose their ability to function when their proteins and/or nucleic acids degrade. This feature is very important for how they are stored.
- Delivery of active sites: Applying liposomes or detergent-lipid particles makes it easier for the encapsulated payload to enter tissues, something that free compounds frequently cannot do.
- Accessibility: Phage embedding in a three-dimensional network is made possible by fibers and hydrogels, which allow for a continuous release of phages to the target region (8).

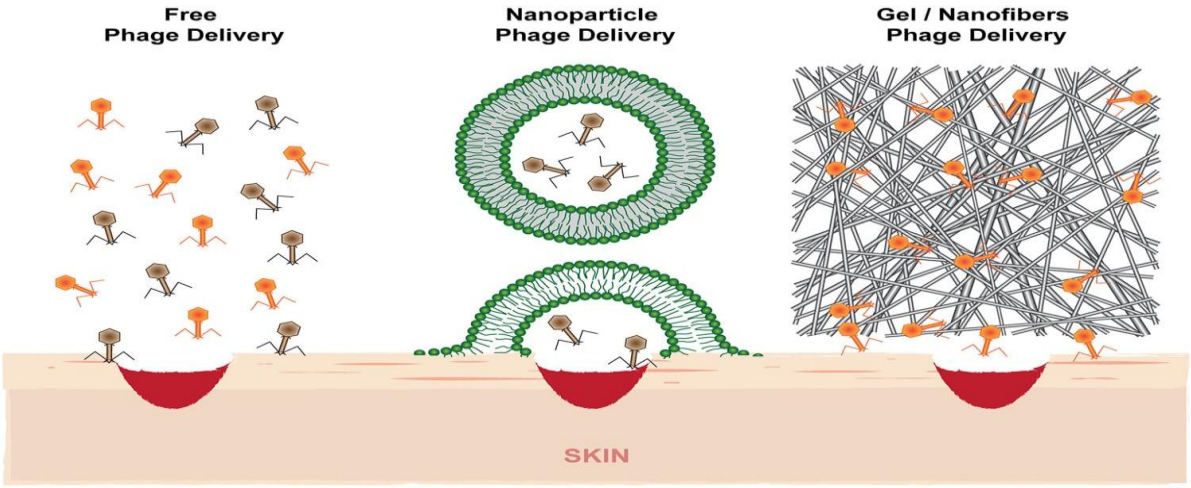

Fig . 1. Illustrate compares three approaches for bacteriophage distribution to the skin: free phages, phages encapsulated in nanoparticles, and phages embedded in a gel or nanofiber matrix to improve stability and delivery (*Figure adapted from Loh et al., 2018; Ref.* 9)

MECHANISMS AND METHODS

Common methods used to produce phage formulations typically rely on encapsulation of some kind. This includes a variety of techniques where bacteriophages are encased in certain stabilizing chemicals that protect the outside world, including emulsification, freeze-drying, spray-drying, liposome encapsulation, and electrospinning. To efficiently target bacterial cells, the phages must be liberated from the substance after encapsulation (10-12).

SPRAY DRYING OF BACTERIOPHAGES

Spray drying is a scalable method for producing stable, dry powder formulations of bacteriophages for use in medical applications, including phage therapy and oral or inhaled dose forms (13-15). This process keeps phages alive during drying and storage by encasing them in protective excipients (16, 17). Spray-dried phage powders can be aerosolized and customized for targeted release to treat respiratory infections (18). The choice of excipients and environmental factors is crucial for long-term stability and effective delivery as shown in figure of spray drying (19, 20).

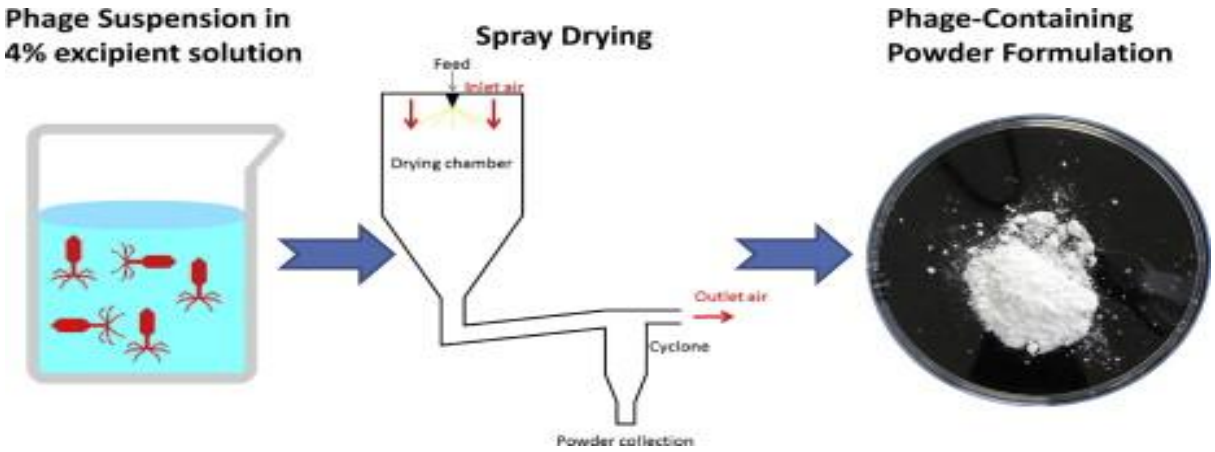

Fig. 2. Shows that to produce a stable, dry powder formulation for potential medical applications, a liquid phage suspension and an excipient solution are fed into a spray dryer. This figure shows how to spray-dry bacteriophages *(Figure adapted fro Vandenheuvel et al., 2013; Ref. 21)*

LIPOSOMES

Researchers are looking into liposomes and nanoparticles as possible targeted delivery systems for the treatment of Salmonella infections (22). However, liposome-encapsulated phages may be less effective if there are issues with phage release or bacterial contact as see in figure 03 of liposomes (23, 24). When combined with liposomes or nanoparticles, hydrogels can provide localized, sustained, and regulated antimicrobial release (25, 26). This can lessen systemic exposure and negative effects while increasing retention at the infection site and potentially improving therapeutic outcomes (27-29).

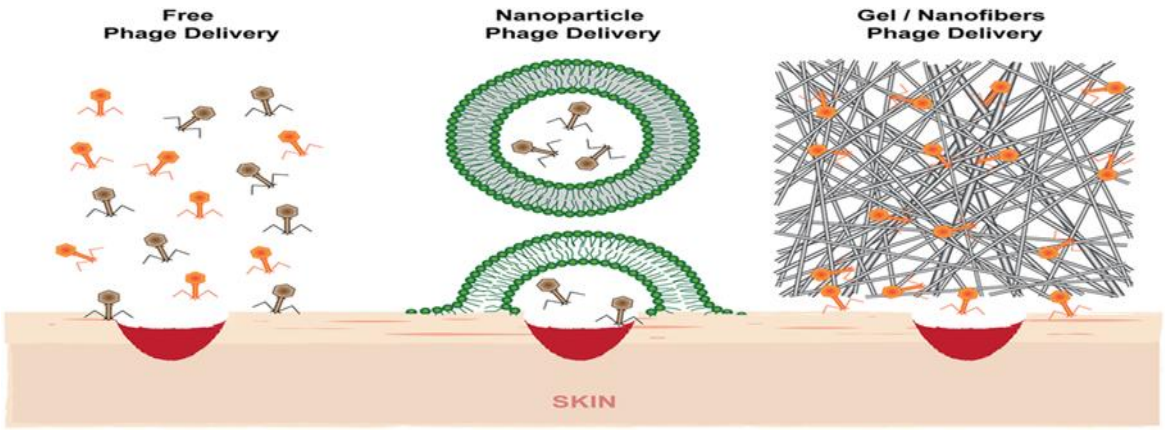

Fig. 3. Illustrates that the topical delivery of phages using delivery systems like liposomes (center) allows particles to penetrate deeper into the infection site than free-phage administration (left). Phages encapsulated in hydrogels or fibers can also release active phage particles over a long period of time because they are integrated in a protective matrix (right).

LYOPHILIZATION (DEHYDRATION PROCESS)

Lyophilization can be used to stabilize and store bacteriophages (30), which is advantageous for both long-term preservation and transportation (31, 32). It involves using stabilizing excipients like mannitol, sucrose, or trehalose to extract water from phage preparations at low pressure and temperature (33). Sucrose and trehalose are helpful supplements that increase phages' infectious time (34, 35). In Fig. 4, the Ccomparison of phages lyophilized by electrospraying (c,f), spray-drying (b,e), and freeze-drying (a,d)

have been illustrated. Spray-drying processes in liquid, vapour, and vapour phases. The choice of excipient, storage temperature, and humidity all affect stability. Encapsulation techniques increase stability and facilitate oral or industrial applications (27, 36).

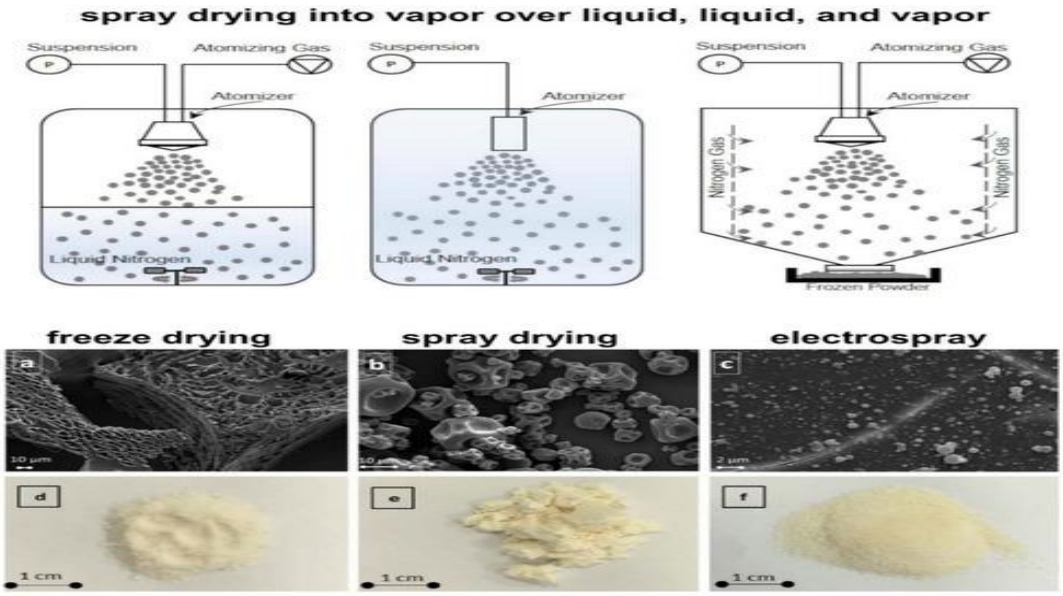

Fig. 4. Comparison of phages lyophilized by electrospraying (c,f), spray-drying (b,e), and freeze-drying (a,d). Spray-drying processes in liquid, vapour, and vapour phases are shown schematically (37). Viral formulations differ significantly between phage powder form and SEM images (38)

MICROENCAPSULATION AND LAYER-BY-LAYER (LBL) COATING

Alginate, chitosan, and pectin are the materials used in microencapsulation (39, 40). Improvements: Added phage resistance with the use of lipid coatings or nanolayers (41-43). Layer-by-layer (LbL) coating, a technique that employs biopolymers to create multilayered thin films with highly adjustable properties for enhanced product protection and storability (44, 45), is used in capsules, drug delivery systems, food preservation, and biomedical devices (46-48).

Benefit: More control over the porosity and bacteriophage-impermeability of the capsule (49).

SMART POLYMER SYSTEMS AND NATURAL POLYMER CARRIERS

React to particular stimuli, such as enzymes or pH. For instance, Eudragit® coatings for colon-specific release disintegrate at pH > 6 (8). Polymeric phage encapsulation has been extensively studied in the treatment of gastrointestinal tract infections (50).

HYDROGEL MATRICES, CELLULOSE–CHITOSAN BEADS, MICROSPHERES

Because hydrogels like GrowDex efficiently store and transport phages while preserving viability and promoting rapid release, they are ideal for high-throughput screening and personalized therapy (51). Probiotics are shielded from heat and acidity stress in food matrices like kefir by encapsulation with cellulose/chitosan hybrid structures. When contrasted to free cells, these beads increase the survivability of probiotics, hence facilitating their usage as targeted delivery systems in nutritional supplements and foods (52).

LIPID-BASED ENCAPSULATION (LIPOSOMES AND TRANSFEROSOMES)

The liposomal phage preparation demonstrated 100% resistance to neutralizing antibodies and maintained its intracellular localization-based lytic activity in macrophages (53). Liposome-encapsulated phages, shielded from antibodies, can infiltrate macrophages and kill bacteria, increasing the efficacy of phage therapy against biofilms and drug-resistant illnesses (54).

NANOPARTICLES, BIOFILM-BASED SYSTEMS, COMBINED METHODS

Silver Nanoparticles (AgNPs) with Phages. A synergistic antibacterial effect is produced when phages and biosynthesized silver nanoparticles are combined. By stabilizing the phages and boosting their

antibacterial action, the nanoparticles present a viable tactic to fight bacteria that are resistant to drugs (55). When administered as biofilms on semi-permeable dextranomer microspheres, probiotics such as Lactobacillus reuteri exhibit greater adhesion to intestinal cells, increased resilience to acidic environments, and increased production of advantageous chemicals. Additionally, this method enables the co-delivery of important nutrients or bioactive compounds that promote probiotic action (56). New materials and technologies have been developed to better protect GI tract phages from biological and chemical threats. These include protecting phages from neutralizing agents, enhancing delivery, and combining antimicrobial chemicals (57-60).

MATERIALS AND METHODS OF ENCAPSULATION

Hydrogel Beads: Gelled beads or microgels have been prepared using calcium pectinate, alginate, and chitosan as the most studied polymers for probiotics encapsulation. Such materials can provide protection of bacteria from gastric acid and release in the intestine. Pectin-chitosan and calcium alginate beads have presented great viability and delivery (61, 62).

STARCH AND PROTEIN-BASED CARRIERS

Blends of arrowroot starch, maltodextrin, and whey protein isolate (WPI) are used as encapsulation matrices singly or in combinations to enhance the effectiveness of probiotics preservation during transit through the gastrointestinal system and even during storage. Blended carriers prepare high encapsulation yields and stability merits gauged due to the combined effects of WPI and MD (63, 64).

GELATIN HYDROGELS

Yeast probiotics, which are encapsulated within hydrogels, have high cell viability under simulated GI conditions. Owing to the chemical cross-linking, the gelatin hydrogels can retain the structure, which serves as an encapsulating layer of delicate seeds (65).

SYNTHETIC MEMBRANES

Polysulfone microtube array membranes (MTAM) are developed to assist in the delivery of probiotics through in situ self-applying patches on the skin. They not only prevent the bacterial leakage of the probiotics, but also ensure that the probiotics remain active (66).

BIOPOLYMERS: POLYSACCHARIDES, PROTEINS, LIPIDS

Food-grade biopolymers are approved natural or synthetic polymers used in food-contact products for their safety and compatibility (67, 68). These substances are used in encapsulation, film formation, and as thickeners and stabilizers across food formulation (68). Ensuring that they meet food-grade requirements is vital for consumer safety and regulatory compliance (67, 68). Polysaccharides: Starch, maltodextrin, gum Arabic, guar gum, chitosan, and alginate (68, 69). Proteins: Gelatin, whey protein, and casein. Lipids: Waxes and fatty acids. Material selection is based on their protective abilities, release behavior, and resistance during processing and storage (6, 68).

EFFECTIVENESS AND APPLICATIONS

GASTROINTESTINAL PROTECTION

Compared to free cells, encapsulation provides dramatically improved survival rates of probiotics in mimicked gastric and intestinal settings, which enables passage of greater amounts of viable bacteria to the large intestine (63).

As demonstrated in trials of allergic asthma, probiotics can also be administered intranasally for focused effects in the respiratory system, broadening the range of tailored probiotic treatments (70).

Complex phage-probiotic interactions can affect gut microbiota dynamics, pathogen management, and the safety, effectiveness, and survival of probiotic use. Probiotics' defence mechanisms against phages, as well as the potential health benefits of combining probiotics with phages, are being investigated (71, 72) and animal production (73).

In animal models, including broiler chickens, the use of phage beverages and probiotics has been demonstrated to enhance growth performance, alter gut microbiota, and boost the quantity of advantageous short-chain fatty acid producers. This mixture can be used in place of growth promoters that contain antibiotics (74).

Phage cocktails that target particular gut bacteria have been shown in vitro to lower harmful populations and encourage the growth of advantageous probiotics such as Lactiplantibacillus plantarum. However, because of things, perhaps phage durability and gut transit, these effects might not necessarily transfer immediately to in vivo conditions (75).

The potential of probiotics and functional foods to enhance health afterward basic dietary requirements is becoming more widely acknowledged. Functional meals are ones that offer extra health advantages, frequently by including bioactive substances or probiotics, which are live microbes. Current studies investigate different food formulas, health impacts, and delivery methods (76-78).

FUNCTIONAL FOOD DEVELOPMENT

Probiotics in encapsulated form can be utilized in dairy and other functional foods, such as yogurt and cheese, due to the maintained viability during the storage period and processing (62, 64). Probiotic microencapsulation can enhance the intestinal barrier function and decrease inflammation in colitis disease models, advocating for their application in functional foods and dietary supplements targeting gut health (79).

DIETETICS AND NUTRITION: MEAT, SEAFOOD, EGGS, FRUITS, VEGETABLES

Technology advancements in dietetics and agriculture have made it more difficult to distribute and stabilize encapsulated bacteriophages, which are vulnerable to denaturation and degradation under a range of conditions: Cleanliness goods Fresh food and surface disinfection Pathogen detection techniques (80). Biocontrol materials that promote the spread of pathogens in specific environments (81).

Meat and seafood: The growth of microorganisms makes perishable foods like meat and seafood more likely to go bad. Bacteriophages and biopolymer coatings can be used in meat model systems to address meat deterioration (82, 83).

Egg: Kim and Chang's 2022 study demonstrates the use of polymer coverings loaded with bacteriophages for egg preservation. They successfully inhibited Salmonella enteritidis by covering chicken eggshells with the PBESE191 phage. After a day, the bacterial reduction was about 2 log10 CFU/g, but bacteriophages could still escape (84).

Fruits and vegetables: A balanced diet requires fruits and vegetables, but their rapid deterioration shortens their shelf life. The food industry faces challenges in preserving some fruits and vegetables due to their high water activity and sugar content, particularly in terms of microbial contamination (85).

Table I. Applications and implications

Area of application	Important takeaways	References
Production of animals	Combinations of phage and probiotics enhance gut health and growth.	(86)
Gut health in humans	Probiotics that are resistant to phages promote safety and colonization.	(86)
Control of infections	Probiotics that are resistant to phages inhibit pathogens; phages have the ability to suppress pathogens and decrease biofilms.	(86)
Safety issues	It has been discovered that phage-mediated gene transfer increases probiotic pathogenicity and may propagate antibiotic resistance.	(87-89)

FOOD INDUSTRY: MICROBIOME MODULATION, PHAGE BIOCONTROL, PRESERVATION OF NUTRITIONAL VALUE

By altering gut flora and restoring normal gut function, phage therapy has been studied to enhance nutritional absorption and digestive health, as demonstrated in a study involving *Clostridium difficile* infections (90). Bacteria-based biocontrol reduces food contamination and guarantees safer nutrition without compromising nutritional value by using phages to prevent infections such as *Salmonella, Listeria,* and *E. coli*

(91). Bacteria-based biocontrol reduces food contamination and guarantees safer nutrition without compromising nutritional value by using phages to prevent infections such as *Salmonella, Listeria,* and *E. coli* (92).

LIMITATIONS AND CHALLENGES

MATERIAL SELECTION AND FOOD-GRADE COMPLIANCE

The type and combination of a given encapsulation material have an impact on encapsulation efficiency, bacterial viability, and release profiles. For instance, chitosan coating has the possibility of reducing probiotic viability because of its antimicrobial properties, depending on concentration and application (93, 94).

STRAIN-DEPENDENT EFFECTS

The encapsulation effectiveness can differ by the strain of probiotics, and some strains may demonstrate greater survival than others under the same encapsulation conditions (61).

ENZYMES THAT BREAK DOWN CAPSULES

Phage-Encoded Depolymerases: Certain bacteriophages have developed depolymerases, which are enzymes that selectively break down bacterial capsules. *Klebsiella* phage KP32, for example, generates depolymerases that target specific capsular serotypes, removing the capsule and boosting the bacteria's susceptibility to phage infection and immune reactions (95, 96).

TRADE-OFFS BETWEEN PHAGE RESISTANCE AND PROBIOTIC FUNCTION

By changing or stopping the synthesis of capsules, bacteria can become resistant to phages. But this frequently has a price: as demonstrated by *Klebsiella pneumoniae* and *Acinetobacter baumannii*, losing the capsule can decrease bacterial pathogenicity and increase sensitivity to host immunological responses.
Bacterial virulence is closely correlated with the existence and shape of capsules, and mutants lacking capsules exhibit a decreased capacity to evade (97).

LEVEL OF PROBIOTIC EFFICACIOUSNESS

It has been demonstrated that microencapsulated probiotics are able to protect the integrity of the intestinal barrier as well as guard against inflammation and oxidative stress even during harsh dietary challenges. This implies that encapsulation not just aids the survival of the bacteria but also enables them to perform their activities effectively once they are in the gut (98).

Table II. Comparative results of probiotics encapsulated and unencapsulated

Form of probiotics unencapsulated (free)	Effectiveness and Survival in the GI Tract	References
Unencapsulated (free)	Because of its susceptibility to severe gastrointestinal disorders, which result in decreased survival rates and less live bacterial transport to the colon, the plant's positive effects are limited.	(99-101)
Encapsulated in microcapsules	By improving protection during GI transit, raising survival rates, and ensuring that more viable bacteria reach the colon, probiotic encapsulation maintains the benefits of probiotics and alters the gut microbiota.	(102-104)

HAZARDS: HORIZONTAL GENE TRANSFER, HOST RANGE LIMITS, VARIABLE OUTCOMES

In situations that initiate phage release, such as antibiotic therapy or quorum sensing signals, phage infection can aid in the spread of virulence genes between bacteria, including probiotics. If harmful genes are acquired by probiotic strains, this could potentially increase their pathogenicity (105).
Environmental factors, bacterial habit (sessile vs. planktonic), as well as the particular strains involved, can all affect how well phage-probiotic combinations work and whether phage resistance develops (106).

PROBIOTIC DELIVERY METHODS THAT EMPHASIZE SELECTIVE RELEASE OR ENCAPSULATION (ENCAPSULATION AND TARGETED RELEASE AS THE MAIN FOCUS OF PROBIOTIC DELIVERY SYSTEMS

Probiotics are frequently encapsulated in hydrogels (such as alginate, gelatin, and pectin) or synthetic polymers (such as polymethacrylates and cellulose sulfate) to secure their viability during gastrointestinal transit and shield them from severe stomach conditions. By releasing viable probiotics into the colon and maintaining structural integrity in acidic environments, these encapsulation techniques improve targeted delivery (107, 108).

The acid and heat resistance of encapsulated probiotics can be further enhanced by combining materials such as cellulose and chitosan, or alginate with xanthan gum. This will increase the probiotics' survival rates throughout gastric transit and preservation in food products (52).

Accuracy and Uses: Improved Survival and Function: Probiotic lifespans under simulated stomach and intestinal circumstances are greatly increased by encapsulation, which frequently leads to a 30–40% rise in viability when compared to free cells (2, 5, 6, 10). Additionally, encapsulated probiotics exhibit increased stability when stored in foods like cheese and kefir (109, 110).

Therapeutic and Functional Foods: These methods of distribution can be used in bioreactor applicati ons, oral supplements, and even functional foods, permitting the creation of goods that periodically supply t he gut with live bacteria (66).

CHALLENGES ASSOCIATED WITH PHAGES IN THE COMPOSITION OF PROBIOTICS

Probiotics and Bacteriophages: Phage Susceptibility By attacking and lowering their viability, resident bacteriophages pose a threat to probiotic bacteria that have been introduced into the gut, compromising colonization and probiotic efficiency (111). This is a major problem for probiotic formulation because immunity to local phages is necessary to optimize colonization (112, 113).

THE IMPACT ON PROBIOTIC SUPERVIVENCE

CAPSULES AS NATURAL PROTECTION AGAINST PHAGES

The probiotic E. coli Nissle 1917 (EcN) gives defense against lytic T4 phage infection through its K5 polysaccharide capsule.(114, 115) Not all commensal E. coli strains have this natural defense mechanism, which is supplied by the capsule and certain lipopolysaccharide (LPS) structures that inactivate phages and stop infection (115).

In mixed cultures, EcN's capsule and LPS can both defend themselves and other *E. coli* strains from phage attack, underscoring the significance of capsule-mediated resistance as an optimal, secure, and effective factor in probiotic design (116-118).

PHAGE DEFENSE THROUGH ENCAPSULATION & BACTERIOPHAGE ENCAPSULATION

Although encapsulation is frequently used to shield probiotics from bile and stomach acid, depending on the encapsulation technique and material, it may also operate as a defense against bacteriophage attack (119, 120).

Probiotic longevity in the gut may be further increased by creating capsules that mimic or strengthen the natural phage resistance (121, 122).

To prevent phages from becoming inactivated and to guarantee targeted distribution, bacteriophages themselves may be encapsulated in liposomes or CaCO3 microparticles in the context of phage treatment. Either the probiotic and phage method of transport must be carefully chosen, though, as certain encased materials can keep phages inactive (123, 124).

ENCAPSULATION OF PHAGES (LIPOSOMES, HYDROGELS, NANOPARTICLES)

Although encapsulation in these systems was investigated, they were unsuitable for delivery since they rendered the phages inactive (125). Phage activity was maintained both prior to and following passage across acidic conditions when encapsulated in CaCO3 microparticles, which makes them a viable oral administration method over the gastrointestinal barrier (126).

Either the encapsulation must be used to keep antigens from escaping from the pellets or to shield them from the fish stomach's acidic environment (127, 128). The bio-encapsulated feed then releases the vaccine into the digestive tract of the fish, which appears to be the most attractive method for releasing vaccines (129). Recent research studies have paid attention to the use of nanoparticles (NPs) as adjuvants and efficient delivery systems in fish vaccine development due to their nano size (130).

The probiotic encapsulation, the protective medium for this type of process is employed to shield the friendly germs when they are stored or pass through the hostile environment of the digestive system to keep them alive and going where they are directed (109, 110). Numerous encapsulation materials and techniques have been developed to improve the viability, stability, and functionality of probiotic organisms in food products, supplements, and pharmaceutical applications (131-133).

THE IMPORTANCE OF CAPSULES IN BACTERIOPHAGE RESISTANCE

Capsules, which have protective coatings of polysaccharides, are frequently used by pathogenic and probiotic bacteria to fend off potential risks such as bacteriophage (phage) attacks. Both the creation of phage-resistant bacterial strains and the formulation of probiotics hinge heavily on the connection between phages and capsules (134, 135).

As a Physical Barrier, Capsules: By acting as a physical barrier, capsules can stop phages from reaching and attaching to the surfaces of bacteria. The probiotic *E. coli* Nissle 1917 (EcN), for example, has a K5 polysaccharide capsule that is essential for its ability to withstand T4 phage infection. Not all *E. coli* strains have this ability, but this capsule with specific lipopolysaccharide (LPS) structures inactivates phages and stops infections (136, 137).

PHAGE-PROBIOTIC INTERACTION MECHANISMS & PHAGE-RESISTANT PROBIOTIC DEVELOPMENT

Phage immunity in Probiotics: Certain probiotic strains, such as *E. coli* Nissle 1917, have built-in defences against phage attacks, such as the K5 capsule and certain lipopolysaccharides. In the gut, since bacteriophages are prevalent, these characteristics aid probiotics in surviving and can even shield additional microbes in mixed cultures against phage infection (123). By engineering or choosing phage-resistant probiotic strains, including phage-resistant Lactobacillus plantarum, their growth, adhesion, and capacity to suppress pathogenic bacteria can be improved, increasing their efficacy in fermentation. Including probiotic strains with innately phage-resistant capsules, like EcN, can improve colonization and survival in the gut, where phages are prevalent (87, 138). Although resistance induced by capsules is advantageous, any compromises with probiotic effectiveness and host contact must be taken into account (123).

DEFENDING PROBIOTICS IN THE GASTROINTESTINAL TRACT

Microencapsulation is regarded as an effective and novel approach intended to improve probiotic survival in the harsh environment of the gastrointestinal tract (99, 102). This advanced method protects the bacteria from disintegrating due to stomach acid and bile before they can successfully access the intestines (139).

INNOVATIONS AND FUTURE DIRECTIONS

ENCAPSULATION ADVANCES: CO-ENCAPSULATION, SIMULTANEOUS ENCAPSULATION, PH-RESPONSIVE AND MUCO-ADHESIVE RELEASE, CONTROLLED RELEASE SYSTEMS

The use of bioactive compounds with encapsulated probiotics, such as charantin, can boost probiotic survivability as well as functionality, like antioxidant properties (64). Simultaneous Encapsulation: Capsule

formation of different strains of probiotics together does not reduce their viability, and may synergistically benefit functional foods (62). Probiotic encapsulation enhances survival through the gastrointestinal tract.

Probiotics are commonly protected using encapsulation methods as they travel through the harsh environment of the gastrointestinal (GI) tract. The primary focus is on ensuring the probiotics survive during digestion, while maintaining their beneficial effects (140-142). In order to provide targeted distribution to the colon, enteric microparticulate formulations that use pH-independent swelling polymers (such as Eudragit biotic and Eudragit RS 100) stay stable in the stomach and release their probiotic payload in the intestine. Intestinal enzymes break down cellulose sulphate microspheres, guaranteeing their release at the intended location (143). Probiotic release can be modulated in time and place to optimize colonization and functional advantages by adjusting the degree of crosslinking, substance makeup, and surface modifications (such as charge alteration of pectin) (108).

NOVEL PHAGE-RESISTANCE STRATEGIES: BLOCKING PHAGE RECEPTORS, EXTRACELLULAR MATRIX PRODUCTION, COMPETITIVE INHIBITORS, RESTRICTION–MODIFICATION SYSTEMS, CRISPR–CAS, ABORTIVE INFECTION SYSTEMS, ENCAPSULATED SPORE-FORMING STRAINS AND BLOCKING OF PHAGE RECEPTORS

Bacteria may change or modify the structure of receptors present on the cell surface, restricting the phage propagation (144). A physical obstruction between phages and their receptors can be created by the production of structured extracellular polymers (145). Naturally occurring molecules in the bacterial environment can specifically attach to the phage receptors, making them unavailable for phages to bind. The principle of the R–M system is to protect the cell against invasion of DNA, including viruses (146). They are an immunity system that works by targeting foreign nucleic acids, including phage genomes and plasmids (147, 148). The three crucial steps of phage multiplication, such as replication, transcription, or translation, are being targeted ABI system (149). Encapsulation is a well-known approach for protecting probiotic cells in other materials, especially polymers (150). Resulting in a physical barrier between the internal phase and its surroundings, helping it to be protected from pH changes, moisture fluctuations, and oxidation (151).

COMBINATION THERAPIES: PHAGE COCKTAILS, GENOMIC AND PHENOTYPIC CHARACTERIZATION, DUAL COATING WITH PHAGE AND ANTIBIOTIC

To decrease the generation of phage-resistant mutants and increase host range, it is becoming more and more usual to use cocktails of several phages, frequently targeting distinct bacterial receptors. Phage-antibiotic combinations can also stop resistance and make MDR organisms more sensitive to antibiotics (152). By using sophisticated genomic tools to monitor phage and bacterial mutations, it is possible to understand how resistance arises (for example, through mutations in efflux pump genes or LPS biosynthesis) and how these alterations can either increase vulnerability to antibiotics or decrease the virulence of bacteria (153).

Dual Coating with Phage and Antibiotic: In animal models of MRSA infection, orthopaedic implants coated with phages and antibiotics (linezolid) in a biopolymer matrix exhibited enhanced healing, reduced inflammation and bacterial adherence, and offered progressive emission. With this method, no resistant mutants appeared (154).

They are employed as safe model viruses for quick screening of novel antiviral materials, while photocatalytic nanoparticles serve as antiviral surface coatings. Phage display devices in high-throughput platforms speed up the identification and assessment of these materials (155).

FUNCTIONAL FOOD INNOVATIONS: PROBIOTIC ENHANCEMENT FOR BIOACTIVITY, ANTIOXIDANT OPTIMIZATION, MOOD AND SLEEP BENEFITS

Dairy-Based Products: Probiotic yoghurts enriched with hydroponically grown ginseng and apple pomace flour exhibit higher sensory qualities, increased antioxidant activity, and possible anti-cancer effects. The ideal 3% apple pomace flour addition to yoghurt increased consumer appeal and health advantages

(156, 157). In experimental models of ulcerative colitis, probiotic cheeses, as Minas Frescal containing Lactococcus lactis, have shown therapeutic benefits (158).

Non-Dairy Substitutes: Lactobacillus fermentum and honey-infused fermented oat-based drinks provide stable probiotic survival and enhanced antioxidant potential, making them a lactose-free nutritional choice (159). If flavoured with isomalt and stevia, without sugar, milk chocolate has been utilised as a matrix to deliver probiotics and omega-3 fatty acids while preserving high probiotic counts and tolerable sensory features (160). Advantages and Strategies for Health: As demonstrated in experiments involving animals with colitis and hypolipidemia, probiotic strains included in functional foods can alter gut microbiota, boost immunological responses, while enhancing gut barrier function (161).

Several probiotic species that have been isolated from processed foods and drinks block the enzymes that break down carbohydrates, which may have antidiabetic effects by regulating blood glucose levels (97). Bioactive and Antioxidant Optimisation: Probiotic fermentation raises the antioxidant activity and total phenolic content of dairy and non-dairy goods, which enhances their beneficial features (97). Effective probiotic strains must cling to intestinal cells, endure gastrointestinal conditions, and demonstrate advantageous metabolic processes. Desirable probiotic features like high hydrophobicity, bile salt tolerance, and antibacterial activity have been demonstrated by strains from a variety of origins such as dairy, processed crops and even vaginal microbiota (162). Protection and Subjective Acceptability: Particular strains are assessed for their capacity to improve the final product's sensory attributes, safety, and absence of pathogenicity (162). Numerous studies in humans as well as animals have shown that adding probiotics to functional foods can increase their metabolic activity and health advantages. Meals enriched with probiotics can enhance the makeup of the gut microbiota, which improves digestion and lessens discomfort in the gut. Probiotics and vitamin B6 together decreased bloating and constipation in lactose-intolerant people and enhanced the good microbes in the gut that aid in lactose digestion (163). Studies have demonstrated that probiotic supplements improve immunological indicators, including elevated cytokine and immunoglobulin levels, and lower inflammation (164). Probiotics improved immunity and changed the gut microbiota towards an improved profile among rodent trials, particularly in elderly participants (165, 166). Biological and Benefits of Metabolism: Probiotics can help animals gain weight, improve feed intake, and enhance nutrient absorption, all of which may benefit human digestion (167). Mood and Sleep Effectiveness: In healthy individuals, taking probiotics has been associated with higher mood, fewer symptoms of depression, and greater quality of sleep, indicating advantages over physical health (167).

REGULATORY AND SAFETY CONSIDERATIONS

GRAS STATUS AND LEGAL BASIS OF ENCAPSULATION MATERIALS

The GRAS classification is necessary in the United States in order to authorize food additives and encapsulating materials. It is supported by scientific studies or a long history of safe use in food before 1958, and it is governed by the Federal Food, Drug, and Cosmetic Act.

ENCAPSULATION MATERIALS WITH GRAS STATUS

Only a selected number of shell-forming substances used in food encapsulation have GRAS approval (67, 68). Common GRAS-certified materials include biopolymers such as proteins (e.g., gelatin, whey protein, zein), polysaccharides (e.g., starch, maltodextrin, gum Arabic, guar gum, chitosan), and lipids (e.g., waxes, fatty acids)(67, 68). Selection depends on application purpose, characteristics of the encapsulated ingredient, and release mechanisms (68).

Carbohydrates like starch, cellulose derivatives, gums, and β-cyclodextrin are widely used and ideal for encasing oxygen-sensitive chemicals due to their neutrality, availability, and protective properties (68). While protein encapsulants like gelatin and whey protein protect contents from oxygen, moisture, light, and unwanted tastes, lipid compounds like waxes and fatty acids encapsulate hydrophobic substances for controlled gastrointestinal release (68).

Though many materials are used in pharmaceutical encapsulation, fewer are authorized for food due to stricter safety standards and GRAS approval requirements. Different regulatory systems across countries also create additional hurdles for international food trade (67).

Obtaining GRAS status demands a detailed evaluation of existing scientific data, including toxicological tests, allergenicity analysis, and assessments of possible chemical migration into food. The FDA mandates that the scientific proof be on par with that required for food additives (68).

STANDARDS FOR FOOD-GRADE BIOPOLYMERS (MIGRATION LIMITS, ALLERGEN LABELING)

Research continues into improving encapsulation functionality for bioactives like probiotics, therapeutic proteins, and peptides (68, 69). New techniques enable targeted, sustained release of active agents (68). However, high production costs and limited availability of GRAS materials limit broader industry adoption (67). Advancements are needed to identify novel GRAS materials and enhance encapsulation processes for food applications (67). Encapsulation materials must consist of monomers and additives authorized in regulatory listings (67, 68). Overall migration must stay within defined thresholds (e.g., 10 mg/dm² per EU regulations) (67, 68).If derived from allergens like soy or gluten, biopolymers must be labeled and assessed for residual allergenic properties

These biopolymers help encapsulate probiotics, enzymes, essential oils, and vitamins, shielding them from environmental hazards and enabling controlled release in digestion (68, 69). For instance, chitosan-coated alginate microcapsules have enhanced probiotic survival under simulated gut conditions (69).

Despite their usefulness, challenges include limited approved options, regulatory complexity, and high costs. Continued research is necessary to innovate new food-safe biopolymers and optimize processes for commercial viability (67). Bacteriophages are viruses that target and destroy bacteria, providing an alternative to antibiotics, especially for multidrug-resistant infections. Although used historically, clinical deployment has been limited by regulatory challenges and the need for validated efficacy (168, 169).

SAFETY OF COMBINING ENCAPSULATION WITH PHAGE THERAPY (MATERIAL SAFETY, COMPLIANCE, VALIDATION)

Phage treatments are considered biological products in the U.S. and must undergo FDA-regulated testing to confirm safety and effectiveness. Similarly, the EMA in Europe applies rigorous standards for phage therapy approval (170).

Preclinical trials: Lab and animal experiments determine phage effectiveness, safety, and side effects (171). These follow Good Clinical Practice (GCP) standards to test safety, dosage, and results in real patients. Obstacles in Clinical Validation (171, 172), their narrow host range may limit application based on bacterial strain and infection site (173).Regulatory complexity: Approval processes vary globally, slowing market entry. Quality control issues: Consistency and purity of phage batches must meet stringent criteria (174).

RECENT INNOVATIONS

New developments include phage cocktails to target broader bacterial groups and CRISPR-edited phages to enhance precision. Ongoing clinical trials are investigating these therapies for difficult infections (175). Encapsulation can protect phages from degradation, control their release, and target them to specific sites in the body. Systems like chitosan-coated alginate capsules, used for probiotics, could be repurposed for phage transport (69).

INTEGRATION RAISES IMPORTANT CONCERNS

Material safety: Only GRAS-certified materials should be used in phage encapsulation for food or pharma use. Food-grade compliance: Encapsulation methods must meet migration and allergen safety criteria. Clinical validation: Encapsulated phage systems also require full preclinical and clinical evaluation.

FINALIZATION AND OPPORTUNITIES

BALANCING RESISTANCE AND PROBIOTIC FUNCTION REMAIN CRITICAL

As multidrug-resistant (MDR) bacterial illnesses increase, phage resistance poses a significant obstacle to the development and use of bacteriophage therapeutics. Numerous new trends, technological gaps, and opportunities in this subject are highlighted by a recent study (176).

Gaps in Innovation: Long-term efficacy may be limited by bacteria developing resistance despite cocktail tactics, occasionally as a result of significant genomic alterations or receptor changes.

The majority of research is preclinical, with few large-scale clinical trials to verify safety, efficacy, and the best ways to deliver the phages to humans.

Host Range Limitations: Many phages have a limited host spectrum, along broad-host-range phages may not cover all clinical isolates, requiring continuous isolation and description of new phages (177).

AGENDA FOR FUTURE RESEARCH

Further study is needed to design new encapsulants, enhance phage stability and release mechanisms, and develop standardized testing protocols. Cooperation across industry, regulators, and academia will be vital for progress (69).

Nutrient-rich foods have a longer shelf life and less bacterial breakdown than medications, which is beneficial for gut health promotion and consumer health (178).

RESULTS

The review article discusses how traditional probiotic distribution is ineffective in cases of severe gastrointestinal conditions. It introduces R-capsule technology, a novel approach that combines bacteriophage-resistant capsules with advanced encapsulating methods to protect probiotics from bacteriophages. Despite the potential for medicinal applications and functional foods, further research is needed to ensure safety and address any possible regulatory concerns.

DISCUSSION

The primary barrier to probiotic distribution is that up to 60% of probiotics can be destroyed by the harsh conditions of the gastrointestinal tract. The study recommends "R-capsules," which are ingenious delivery systems that provide dual defense against the GI environment and bacteriophages, as a workaround for this. These capsules release probiotics in response to specific triggers and use bacteriophages to specifically target harmful bacteria. The review concludes that by combining phage technology with state-of-the-art encapsulation platforms, as well as new materials and procedures, probiotic efficacy may be significantly increased and their medicinal uses may be expanded. It is also emphasized how important it is to select probiotic strains with naturally occurring phage-resistant capsules in order to improve their survival and gut colonization.

FUTURE PERSPECTIVES

The primary objectives of customized probiotic delivery in the future are disease prevention and precise microbiome modification. This will be achieved through the use of innovative non-oral delivery methods, synergistic phage-probiotic systems, advanced encapsulation for targeted release, and customized treatments. Important problems that must be solved include increasing production and proving the effectiveness and safety of phage-based systems for people.

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References:

1. Verna EC, Lucak SJTaig. Use of probiotics in gastrointestinal disorders: what to recommend? Therapeutic Advances in Gastroenterology. 2010;3(5):307-19.
2. Govender M, Choonara YE, Kumar P, du Toit LC, van Vuuren S, Pillay VJAP. A review of the advancements in probiotic delivery: Conventional vs. non-conventional formulations for intestinal flora supplementation. AAPS PharmSciTech. 2014;15:29-43.
3. Li C, Wang ZX, Xiao H, Wu FGJAM. Intestinal delivery of probiotics: materials, strategies, and applications Advanced Materials. 2024;36(32):2310174.
4. Wang Z-D, Zhang W, Liang T-XJP. Advancements in Oral Delivery Systems for Probiotics Based on Polysaccharides. Polymers.2025;17(2):144.
5. Wolfe W, Xiang Z, Yu X, Li P, Chen H, Yao M, et al. The challenge of applications of probiotics in gastrointestinal diseases. Advanced Gut & Microbiome Research. 2023;2023(1):1984200.
6. Sultana K, Godward G, Reynolds N, Arumugaswamy R, Peiris P, Kailasapathy KJIjofm. Encapsulation of probiotic bacteria with alginate–starch and evaluation of survival in simulated gastrointestinal conditions and in yoghurt. International Journal of Food Microbiology. 2000;62(1-2):47-55.
7. Pereira EPR, da Graça JS, Ferreira BM, Balthazar CF, Xavier-Santos D, Bezerril FF, et al. What are the main obstacles to turning foods healthier through probiotics incorporation? a review of functionalization of foods by probiotics and bioactive metabolites. Food Research International. 2024;176:113785.
8. Loh B, Gondil VS, Manohar P, Khan FM, Yang H, Leptihn SJA, et al. Encapsulation and delivery of therapeutic phages. Applied and Environmental Microbiology. 2021;87(5):e01979-20.
9. Loh B, Gondil V, Manohar P, Khan F, Yang H, Leptihn S. Encapsulation and Delivery of Therapeutic Phages. Applied and Environmental Microbiology. 2020;87.
10. Batalha LS, Gontijo MTP, De Carvalho Teixeira AVN, Boggione DMG, Lopez MS, Eller MR, et al. Encapsulation in alginate-polymers improves stability and allows controlled release of the UFV-AREG1 bacteriophage. Food research international. 2021;139:109947.
11. Cortés P, Cano-Sarabia M, Colom J, Otero J, Maspoch D, Llagostera M. Nano/microformulations for Bacteriophage Delivery. Methods in molecular biology. 2024;2734:117-30.
12. Otero J, García-Rodríguez A, Cano-Sarabia M, Maspoch D, Marcos R, Cortés P, et al. Biodistribution of Liposome-Encapsulated Bacteriophages and Their Transcytosis During Oral Phage Therapy. Frontiers in Microbiology. 2019;10.
13. Malik D. Bacteriophage Encapsulation Using Spray Drying for Phage Therapy. Current issues in molecular biology. 2020;40:303-16.
14. Chang R, Wong J, Mathai A, Morales S, Kutter E, Britton W, et al. Production of highly stable spray dried phage formulations for treatment of Pseudomonas aeruginosa lung infection. European Journal of Pharmaceutics and Biopharmaceutics. 2017;121:1.
15. Vinner G, Rezaie-Yazdi Z, Leppanen M, Stapley A, Leaper M, Malik D. Microencapsulation of Salmonella-Specific Bacteriophage Felix O1 Using Spray-Drying in a pH-Responsive Formulation and Direct Compression Tableting of Powders into a Solid Oral Dosage Form. Pharmaceuticals. 2019;12.
16. Leung S, Parumasivam T, Gao F, Carrigy N, Vehring R, Finlay W, et al. Production of Inhalation Phage Powders Using Spray Freeze Drying and Spray Drying Techniques for Treatment of Respiratory Infections. Pharmaceutical Research. 2016;33:1486-96.
17. Yan W, He R, Tang X, Tian B, Liu Y, Tong Y. The Influence of Formulation Components and Environmental Humidity on Spray-Dried Phage Powders for Treatment of Respiratory Infections Caused by Acinetobacter baumannii. Pharmaceutics. 2021;13.

18. Leung S, Parumasivam T, Gao F, Carter E, Carrigy N, Vehring R. Effects of storage conditions on the stability of spray dried, inhalable bacteriophage powders. International journal of pharmaceutics. 2017;521 1-2:141-9.
19. Leung S, Parumasivam T, Nguyen A, Gengenbach T, Carter E, Carrigy N. Effect of storage temperature on the stability of spray dried bacteriophage powders. European Journal of Pharmaceutics and Biopharmaceutics. 2018;127:213.
20. Ergin F. Effect of freeze drying, spray drying and electrospraying on the morphological, thermal, and structural properties of powders containing phage Felix O1 and activity of phage Felix O1 during storage. Powder Technology. 2022.
21. Vandenheuvel D, Singh A, Vandersteegen K, Klumpp J, Lavigne R, Van den Mooter G. Feasibility of spray drying bacteriophages into respirable powders to combat pulmonary bacterial infections. European Journal of Pharmaceutics and Biopharmaceutics. 2013;84(3):578-82.
22. Vanić Ž, Jøraholmen MW, Škalko-Basnet N. Challenges and considerations in liposomal hydrogels for the treatment of infection. Expert Opinion on Drug Delivery. 2025;22:255-76.
23. Gao W, Vecchio D, Li J, Zhu J, Zhang Q, Fu V, et al. Hydrogel Containing Nanoparticle-Stabilized Liposomes for Topical Antimicrobial Delivery. ACS Nano. 2014;8:2900-7.
24. Yang P, Li J, Xiumei, Hu N, Song Z, Chen B, et al. Novel delivery systems for phages and lysins in the topical management of wound infections: a narrative review. Frontiers in Microbiology. 2025;16.
25. Elkhoury K, Koçak P, Kang A, Arab-Tehrany E, Ward JE, Shin S. Engineering Smart Targeting Nanovesicles and Their Combination with Hydrogels for Controlled Drug Delivery. Pharmaceutics. 2020;12.
26. Ahmad N, Bukhari SNA, Hussain M, Ejaz H, Munir MU, Amjad MW. Nanoparticles incorporated hydrogels for delivery of antimicrobial agents: developments and trends. RSC Advances. 2024;14:13535-64.
27. Wdowiak M, Paczesny J, Raza SJP. Enhancing the stability of bacteriophages using physical, chemical, and nano-based approaches: A review. 2022;14(9):1936.
28. Binaymotlagh R, Haghighi FH, Chronopoulou L, Palocci C. Liposome–Hydrogel Composites for Controlled Drug Delivery Applications. Gels. 2024;10.
29. Furlani F, Rossi A, Grimaudo M, Bassi G, Giusto E, Molinari F, et al. Controlled Liposome Delivery from Chitosan-Based Thermosensitive Hydrogel for Regenerative Medicine. International Journal of Molecular Sciences. 2022;23.
30. Manohar P, Ramesh N. Improved lyophilization conditions for long-term storage of bacteriophages. Scientific Reports. 2019;9.
31. Zhang Y, Peng X, Zhang H, Watts A, Ghosh D. Manufacturing and ambient stability of shelf freeze dried bacteriophage powder formulations. International Journal of Pharmaceutics. 2018;542:1.
32. Merabishvili M, Vervaet C, Pirnay J, De Vos D, Verbeken G, Mast J, et al. Stability of Staphylococcus aureus Phage ISP after Freeze-Drying (Lyophilization). PLoS ONE. 2013;8.
33. Liang L, Carrigy N, Kariuki S, Muturi P, Onsare R, Nagel T, et al. Development of a Lyophilization Process for Campylobacter Bacteriophage Storage and Transport. Microorganisms. 2020;8.
34. González-Menéndez E, Fernández L, Gutiérrez D, Rodríguez A, Martínez B, García P. Comparative analysis of different preservation techniques for the storage of Staphylococcus phages aimed for the industrial development of phage-based antimicrobial products. PLoS ONE. 2018;13.
35. Śliwka P, Skaradziński G, Dusza I, Grzywacz A, Skaradzińska A. Freeze-Drying of Encapsulated Bacteriophage T4 to Obtain Shelf-Stable Dry Preparations for Oral Application. Pharmaceutics. 2023;15.
36. Puapermpoonsiri U, Ford S, Van Der Walle C. Stabilization of bacteriophage during freeze drying. International journal of pharmaceutics. 2010;389 1-2:168-75.
37. Adali MB, Barresi AA, Boccardo G, Pisano R. Spray freeze-drying as a solution to continuous manufacturing of pharmaceutical products in bulk. Processes. 2020;8(6):709.
38. Ergin F. Effect of freeze drying, spray drying and electrospraying on the morphological, thermal, and structural properties of powders containing phage Felix O1 and activity of phage Felix O1 during storage. Powder Technology. 2022;404:117516.
39. Ji R, Wu J, Zhang J-L, Wang T, Zhang X-D, Shao L, et al. Extending Viability of Bifidobacterium longum in Chitosan-Coated Alginate Microcapsules Using Emulsification and Internal Gelation Encapsulation Technology. Frontiers in Microbiology. 2019;10.
40. Wani S, Ali M, Mehdi S, Masoodi M, Zargar M, Shakeel F. A review on chitosan and alginate-based microcapsules: Mechanism and applications in drug delivery systems. International journal of biological macromolecules. 2023:125875.

41. Călinoiu L, Ștefănescu B, Pop I, Muntean L, Vodnar D. Chitosan Coating Applications in Probiotic Microencapsulation. Coatings. 2019.
42. Rizo-Vázquez F, Vázquez-Ovando A, Mejía-Reyes D, Gálvez-López D, Rosas-Quijano R. Use of Lactulose as Prebiotic and Chitosan Coating for Improvement the Viability of Lactobacillus sp. FM4.C1.2 Microencapsulate with Alginate. Processes. 2024.
43. Parsana Y, Yadav M, Kumar S. Microencapsulation in the chitosan-coated alginate-inulin matrix of Limosilactobacillus reuteri SW23 and Lactobacillus salivarius RBL50 and their characterization. Carbohydrate Polymer Technologies and Applications. 2023.
44. Escobar A, Muzzio N, Moya S. Antibacterial Layer-by-Layer Coatings for Medical Implants. Pharmaceutics. 2020;13.
45. Arnon-Rips H, Poverenov E. Improving food products' quality and storability by using Layer by Layer edible coatings. Trends in Food Science and Technology. 2018;75:81-92.
46. Akkuş-Dağdeviren ZB, Fürst A, Friedl JD, Tribus M, Bernkop-Schnürch A. Nanoarchitectonics of Layer-by-Layer (LbL) coated nanostructured lipid carriers (NLCs) for Enzyme-Triggered charge reversal. Journal of colloid and interface science. 2022;629 Pt A:541-53.
47. Gnanasampanthan T, Beyer C, Yu W, Karthäuser J, Wanka R, Spöllmann S, et al. Effect of Multilayer Termination on Nonspecific Protein Adsorption and Antifouling Activity of Alginate-Based Layer-by-Layer Coatings. Langmuir : the ACS journal of surfaces and colloids. 2021.
48. Carosio F, Alongi J. Ultra-Fast Layer-by-Layer Approach for Depositing Flame Retardant Coatings on Flexible PU Foams within Seconds. ACS applied materials & interfaces. 2016;8 10:6315-9.
49. Thaher YA, Abdelghany S, Abulateefeh S. pH-responsive LBL coated silica nanocarriers for controlled release of chlorhexidine. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2023.
50. Soliman WS, Shaapan RM, Mohamed LA, Gayed SSJOvj. Recent biocontrol measures for fish bacterial diseases, in particular to probiotics, bio-encapsulated vaccines, and phage therapy. 2019;9(3):190–5-–5.
51. Patpatia S, Schaedig E, Dirks A, Paasonen L, Skurnik M, Kiljunen SJFiC, et al. Rapid hydrogel-based phage susceptibility test for pathogenic bacteria. 2022;12:1032052.
52. Afzaal M, Saeed F, Ateeq H, Shah YA, Hussain M, Javed A, et al. Effect of cellulose–chitosan hybrid-based encapsulation on the viability and stability of probiotics under simulated gastric transit and in kefir. 2022;7(3):109.
53. Gondil VS, Chhibber SJFiP. Bacteriophage and endolysin encapsulation systems: a promising strategy to improve therapeutic outcomes. 2021;12:675440.
54. Singla S, Harjai K, Katare OP, Chhibber SJPO. Encapsulation of bacteriophage in liposome accentuates its entry in to macrophage and shields it from neutralizing antibodies. 2016;11(4):e0153777.
55. Abdelsattar AS, Nofal R, Makky S, Safwat A, Taha A, El-Shibiny AJA. The synergistic effect of biosynthesized silver nanoparticles and phage zcse2 as a novel approach to combat multidrug-resistant salmonella enterica. 2021;10(6):678.
56. Kim H, Jang JH, Jung IY, Kim HR, Cho JHJB. Novel genetically engineered probiotics for targeted elimination of Pseudomonas aeruginosa in intestinal colonization. 2023;11(10):2645.
57. Vinner G, Vladisavljević G, Clokie M, Malik D. Microencapsulation of Clostridium difficile specific bacteriophages using microfluidic glass capillary devices for colon delivery using pH triggered release. PLoS ONE. 2017;12.
58. Luong T, Salabarria A-C, Roach D. Phage Therapy in the Resistance Era: Where Do We Stand and Where Are We Going? Clinical therapeutics. 2020.
59. Gutiérrez B, Domingo-Calap P. Phage Therapy in Gastrointestinal Diseases. Microorganisms. 2020;8.
60. Hasan M, Ahn J. Evolutionary Dynamics between Phages and Bacteria as a Possible Approach for Designing Effective Phage Therapies against Antibiotic-Resistant Bacteria. Antibiotics. 2022;11.
61. Yeung TW, Üçok EF, Tiani KA, McClements DJ, Sela DAJFim. Microencapsulation in alginate and chitosan microgels to enhance viability of Bifidobacterium longum for oral delivery. 2016;7:494.
62. Vinceković M, Bandić LM, Oštarić F, Kiš M, Zdolec N, Marić I, et al. Simultaneous Encapsulation of Probiotic Bacteria (Lactococcus lactis, and Lactiplantibacillus plantarum) in Calcium Alginate Hydrogels. 2025;11(1):34.
63. Samedi L, Charles ALJF. Viability of 4 probiotic bacteria microencapsulated with arrowroot starch in the simulated gastrointestinal tract (GIT) and yoghurt. 2019;8(5):175.
64. Massounga Bora AF, Li X, Liu LJF. Physicochemical and functional characterization of newly designed biopolymeric-based encapsulates with probiotic culture and charantin. 2021;10(11):2677.

65. Patarroyo JL, Florez-Rojas JS, Pradilla D, Valderrama-Rincón JD, Cruz JC, Reyes LHJP. Formulation and characterization of gelatin-based hydrogels for the encapsulation of Kluyveromyces lactis—Applications in packed-bed reactors and probiotics delivery in humans. 2020;12(6):1287.
66. Yang A-J, Marito S, Yang J-J, Keshari S, Chew C-H, Chen C-C, et al. A microtube array membrane (MTAM) encapsulated live fermenting Staphylococcus epidermidis as a skin probiotic patch against Cutibacterium acnes. 2018;20(1):14.
67. Stark K, Hitchcock JP, Fiaz A, White AL, Baxter EA, Biggs S, et al. Encapsulation of emulsion droplets with metal shells for subsequent remote, triggered release. 2019;11(13):12272-82.
68. Timilsena YP, Haque MA, Adhikari BJF, Sciences N. Encapsulation in the food industry: A brief historical overview to recent developments. 2020;11(6):481-508.
69. Sun Q, Yin S, He Y, Cao Y, Jiang CJN. Biomaterials and encapsulation techniques for probiotics: Current status and future prospects in biomedical applications. 2023;13(15):2185.
70. Spacova I, Petrova M, Fremau A, Pollaris L, Vanoirbeek J, Ceuppens J, et al. Intranasal administration of probiotic Lactobacillus rhamnosus GG prevents birch pollen-induced allergic asthma in a murine model. 2019;74(1):100-10.
71. Nagarajan V, Peng M, Tabashsum Z, Salaheen S, Padilla J, Biswas D. Antimicrobial Effect and Probiotic Potential of Phage Resistant Lactobacillus plantarum and its Interactions with Zoonotic Bacterial Pathogens. Foods. 2019;8.
72. Liu CG, Green S, Min L, Clark J, Salazar K, Terwilliger A, et al. Phage-Antibiotic Synergy Is Driven by a Unique Combination of Antibacterial Mechanism of Action and Stoichiometry. mBio. 2020;11.
73. Nagarajan V, Peng M, Tabashsum Z, Salaheen S, Padilla J, Biswas DJF. Antimicrobial effect and probiotic potential of phage resistant Lactobacillus plantarum and its interactions with zoonotic bacterial pathogens. 2019;8(6):194.
74. Shaufi MAM, Sieo CC, Chong CW, Geok Hun T, Omar AR, Han Ming G, et al. Effects of phage cocktail, probiotics, and their combination on growth performance and gut microbiota of broiler chickens. 2023;13(8):1328.
75. Buttimer C, Sutton T, Colom J, Murray E, Bettio PH, Smith L, et al. Impact of a phage cocktail targeting Escherichia coli and Enterococcus faecalis as members of a gut bacterial consortium in vitro and in vivo. 2022;13:936083.
76. Peng M, Tabashsum Z, Anderson M, Truong A, Houser A, Padilla J, et al. Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. Comprehensive reviews in food science and food safety. 2020;19 4:1908-33.
77. Ashaolu T. Immune boosting functional foods and their mechanisms: A critical evaluation of probiotics and prebiotics. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2020;130:110625.
78. Obayomi OV, Olaniran AF, Owa SO. Unveiling the role of functional foods with emphasis on prebiotics and probiotics in human health: A review. Journal of Functional Foods. 2024.
79. Wang H, Sun Y, Ma X, Yang T, Wang FJN. The lactobacillus plantarum P-8 probiotic microcapsule prevents DSS-induced colitis through improving intestinal integrity and reducing colonic inflammation in mice. 2024;16(7):1055.
80. Jamaledin R, Sartorius R, Di Natale C, Onesto V, Manco R, Mollo V, et al. PLGA microparticle formulations for tunable delivery of a nano-engineered filamentous bacteriophage-based vaccine: in vitro and in silico-supported approach. Journal of Nanostructure in Chemistry. 2023:1-16.
81. Hussain MA, Liu H, Wang Q, Zhong F, Guo Q, Balamurugan SJCrifs, et al. Use of encapsulated bacteriophages to enhance farm to fork food safety. 2017;57(13):2801-10.
82. Tidim G, Guzel M, Soyer Y, Erel-Goktepe I. Layer-by-layer assembly of chitosan/alginate thin films containing Salmonella enterica bacteriophages for antibacterial applications. Carbohydrate polymers. 2023;328:121710.
83. Moura-Alves M, Esteves A, Ciríaco M, Silva J, Saraiva C. Antimicrobial and Antioxidant Edible Films and Coatings in the Shelf-Life Improvement of Chicken Meat. Foods. 2023;12.
84. Kızal B, Ayaz N, Çufaoğlu G, Göncüoğlu M. CONTROL OF SALMONELLA ENTERITIDIS AND SALMONELLA KENTUCKY ON EGGSHELL WITH BACTERIOPHAGE APPLICATION. Journal of Applied Biological Sciences. 2024.
85. Rindhe S, Khan A, Priyadarshi R, Chatli M, Wagh R, Kumbhar V, et al. Application of bacteriophages in biopolymer-based functional food packaging films. 2024;23(3):e13333.
86. Forsyth J, Barron N, Scott L, Watson B, Chisnall M, Meaden S, et al. Decolonizing drug-resistant E. coli with phage and probiotics: breaking the frequency-dependent dominance of residents. Microbiology. 2023;169.

87. Tóth A, Csabai I, Judge MF, Maróti G, Becsei Á, Spisák S, et al. Mobile Antimicrobial Resistance Genes in Probiotics. Antibiotics. 2021;10.
88. González-Villalobos E, Balcázar J. Does phage-mediated horizontal gene transfer represent an environmental risk? Trends in microbiology. 2022.
89. Daniali M, Nikfar S, Abdollahi M. Antibiotic resistance propagation through probiotics. Expert Opinion on Drug Metabolism & Toxicology. 2020;16:1207-15.
90. Jaglan AB, Anand T, Verma R, Vashisth M, Virmani N, Bera B, et al. Tracking the phage trends: a comprehensive review of applications in therapy and food production. 2022;13:993990.
91. Moye Z, Woolston J, Sulakvelidze A. Bacteriophage Applications for Food Production and Processing. Viruses. 2018;10.
92. Hosseini A, Saba MK, Watkins C. Microbial antagonists to biologically control postharvest decay and preserve fruit quality. Critical Reviews in Food Science and Nutrition. 2023;64:7330-42.
93. Yasmin I, Saeed M, Pasha I, Zia M. Development of Whey Protein Concentrate-Pectin-Alginate Based Delivery System to Improve Survival of B. longum BL-05 in Simulated Gastrointestinal Conditions. Probiotics and Antimicrobial Proteins. 2019;11:413-26.
94. Rojas-Muñoz Y, Santagapita P, Quintanilla-Carvajal M. Probiotic Encapsulation: Bead Design Improves Bacterial Performance during In Vitro Digestion. Polymers. 2023;15.
95. Abdelkader K, Gutiérrez D, Latka A, Boeckaerts D, Drulis-Kawa Z, Criel B, et al. The Specific Capsule Depolymerase of Phage PMK34 Sensitizes Acinetobacter baumannii to Serum Killing. Antibiotics. 2022;11.
96. Łubkowska B, Czajkowska E, Stodolna A, Sroczynski M, Zylicz-Stachula A, Sobolewski I, et al. A novel thermostable TP-84 capsule depolymerase: a method for rapid polyethyleneimine processing of a bacteriophage-expressed proteins. Microbial Cell Factories. 2023;22.
97. Song L, Yang X, Huang J, Zhu X, Han G, Wan Y, et al. Phage selective pressure reduces virulence of hypervirulent Klebsiella pneumoniae through mutation of the wzc gene. 2021;12:739319.
98. Abuqwider J, Di Porzio A, Barrella V, Gatto C, Sequino G, De Filippis F, et al. Limosilactobacillus reuteri DSM 17938 reverses gut metabolic dysfunction induced by Western diet in adult rats. 2023;10:1236417.
99. Da Silva MN, Tagliapietra B, Flores VDA, Richards NSPDS. In vitro test to evaluate survival in the gastrointestinal tract of commercial probiotics. Current Research in Food Science. 2021;4:320-5.
100. Arnal M, Denis S, Uriot O, Lambert C, Holowacz S, Paul F, et al. Impact of oral galenic formulations of Lactobacillus salivarius on probiotic survival and interactions with microbiota in human in vitro gut models. Beneficial microbes. 2021:1-16.
101. Morelli L, Pellegrino P. A critical evaluation of the factors affecting the survival and persistence of beneficial bacteria in healthy adults. Beneficial microbes. 2021:1-12.
102. Govaert M, Rotsaert C, Vannieuwenhuyse C, Duysburgh C, Medlin S, Marzorati M, et al. Survival of Probiotic Bacterial Cells in the Upper Gastrointestinal Tract and the Effect of the Surviving Population on the Colonic Microbial Community Activity and Composition. Nutrients. 2024;16.
103. Bernatek M, Żukiewicz-Sobczak W, Lachowicz-Wiśniewska S, Piątek J. Factors Determining Effective Probiotic Activity: Evaluation of Survival and Antibacterial Activity of Selected Probiotic Products Using an "In Vitro" Study. Nutrients. 2022;14.
104. Rajam R, Subramanian P. Encapsulation of probiotics: past, present and future. Beni-Suef University Journal of Basic and Applied Sciences. 2022;11.
105. Rossmann FS, Racek T, Wobser D, Puchalka J, Rabener EM, Reiger M, et al. Phage-mediated dispersal of biofilm and distribution of bacterial virulence genes is induced by quorum sensing. 2015;11(2):e1004653.
106. Ulrich L, Giez C, Steiner LX, Hentschel U, Lachnit TJFiM. Adaptive lifestyle of bacteria determines phage-bacteria interaction. 2022;13:1056388.
107. Yus C, Gracia R, Larrea A, Andreu V, Irusta S, Sebastian V, et al. Targeted release of probiotics from enteric microparticulated formulations. 2019;11(10):1668.
108. Sun Q, Wicker LJF. Hydrogel encapsulation of lactobacillus casei by block charge modified pectin and improved gastric and storage stability. 2021;10(6):1337.
109. Han J, McClements D, Liu X, Liu F. Oral delivery of probiotics using single-cell encapsulation. Comprehensive reviews in food science and food safety. 2024;23 3.
110. Yao M, Xie J, Du H, McClements D, Xiao H, Li L. Progress in microencapsulation of probiotics: A review. Comprehensive reviews in food science and food safety. 2020;19 2:857-74.

111. Vitetta L, Vitetta G, Hall S. Immunological Tolerance and Function: Associations Between Intestinal Bacteria, Probiotics, Prebiotics, and Phages. Frontiers in Immunology. 2018;9.
112. Kim J, Hosseindoust A, Lee S, Choi Y, Kim M, Lee J, et al. Bacteriophage cocktail and multi-strain probiotics in the feed for weanling pigs: effects on intestine morphology and targeted intestinal coliforms and Clostridium. Animal : an international journal of animal bioscience. 2017;11 1:45-53.
113. Neschislyaev V, Shilova E, Nikolaeva A, Orlova E. Study of a combined biological product with antibacterial and probiotic activity. Biological Products Prevention, Diagnosis, Treatment. 2023.
114. Soundararajan M, Von Bünau R, Oelschlaeger T. K5 Capsule and Lipopolysaccharide Are Important in Resistance to T4 Phage Attack in Probiotic E. coli Strain Nissle 1917. Frontiers in Microbiology. 2019;10.
115. Bryan D, El-Shibiny A, Hobbs Z, Porter J, Kutter E. Bacteriophage T4 Infection of Stationary Phase E. coli: Life after Log from a Phage Perspective. Frontiers in Microbiology. 2016;7.
116. Millman A, Bernheim A, Stokar-Avihail A, Fedorenko T, Voichek M, Leavitt A, et al. Bacterial Retrons Function In Anti-Phage Defense. Cell. 2020;183:1551-61.
117. Gaborieau B, Delattre R, Adiba S, Clermont O, Denamur E, Ricard J, et al. Variable fitness effects of bacteriophage resistance mutations in Escherichia coli: implications for phage therapy. Journal of Virology. 2024;98.
118. Wu Y, Garushyants S, Van Den Hurk A, Aparicio-Maldonado C, Kushwaha S, King C, et al. Bacterial defense systems exhibit synergistic anti-phage activity. Cell host & microbe. 2024.
119. Colom J, Cano-Sarabia M, Otero J, Cortés P, Maspoch D, Llagostera M. Liposome-Encapsulated Bacteriophages for Enhanced Oral Phage Therapy against Salmonella spp. Applied and Environmental Microbiology. 2015;81:4841-9.
120. Wang R, Yeh Y-J, An Y-N, Virly. Engineering pH-sensitive erodible chitosan hydrogel composite containing bacteriophage: An interplay between hydrogel and bacteriophage against Staphylococcus aureus. International journal of biological macromolecules. 2023:127371.
121. Dini C, Islan G, De Urraza P, Castro G. Novel biopolymer matrices for microencapsulation of phages: enhanced protection against acidity and protease activity. Macromolecular bioscience. 2012;12 9:1200-8.
122. Malik D, Sokolov I, Vinner G, Mancuso F, Cinquerrui S, Vladisavljević G, et al. Formulation, stabilisation and encapsulation of bacteriophage for phage therapy. Advances in colloid and interface science. 2017;249:100-33.
123. Soundararajan M, von Bünau R, Oelschlaeger TAJFiM. K5 capsule and lipopolysaccharide are important in resistance to T4 phage attack in probiotic E. coli strain Nissle 1917. 2019;10:2783.
124. Cinquerrui S, Mancuso F, Vladisavljević GT, Bakker SE, Malik DJJFim. Nanoencapsulation of bacteriophages in liposomes prepared using microfluidic hydrodynamic flow focusing. 2018;9:2172.
125. Volodkin D, Petrov A, Prevot M, Sukhorukov G. Matrix polyelectrolyte microcapsules: new system for macromolecule encapsulation. Langmuir : the ACS journal of surfaces and colloids. 2004;20 8:3398-406.
126. Musin EV, Kim AL, Dubrovskii AV, Ariskina EV, Kudryashova EB, Tikhonenko SAJP. The pathways to create containers for bacteriophage delivery. 2022;14(3):613.
127. Wang C, Tang H, Duan Y, Zhang Q, Shan W, Wang X, et al. Oral biomimetic virus vaccine hydrogel for robust abscopal antitumour efficacy. Journal of colloid and interface science. 2024;674:92-107.
128. Yang F, Meng L, Lin S, Wu F, Liu J. Polyethyleneimine-complexed charge-reversed yeast cell walls for the enhanced oral delivery of pseudovirus-based antigens. Chemical communications. 2021.
129. Zhao Z, Qiao S, Jin Z, Li H, Yu H, Zhang C, et al. Acidified sucralfate encapsulated chitosan derivative nanoparticles as oral vaccine adjuvant delivery enhancing mucosal and systemic immunity. International journal of biological macromolecules. 2024:135424.
130. Costa MJ, Pastrana LM, Teixeira JA, Sillankorva SM, Cerqueira MAJV. Bacteriophage delivery systems for food applications: Opportunities and perspectives. 2023;15(6):1271.
131. Zhang C, Gao X, Ren X, Xu T, Peng Q, Zhang Y, et al. Bacteria-Induced Colloidal Encapsulation for Probiotic Oral Delivery. ACS nano. 2023.
132. Xu C, Ban Q, Wang W, Hou J, Jiang Z-M. Novel nano-encapsulated probiotic agents: Encapsulate materials, delivery, and encapsulation systems. Journal of controlled release : official journal of the Controlled Release Society. 2022.
133. Gu Q, Yin Y, Yan X, Liu X, Liu F, McClements D. Encapsulation of multiple probiotics, synbiotics, or nutrabiotics for improved health effects: A review. Advances in colloid and interface science. 2022;309:102781.
134. Altamirano FG, Forsyth J, Patwa R, Kostoulias X, Trim M, Subedi D, et al. Bacteriophage-resistant Acinetobacter baumannii are resensitized to antimicrobials. Nature Microbiology. 2021;6:157-61.

135. Rendueles O, De Sousa JM, Rocha E. Competition between lysogenic and sensitive bacteria is determined by the fitness costs of the different emerging phage-resistance strategies. eLife. 2023;12.
136. Bai J, Raustad N, Denoncourt J, Van Opijnen T, Geisinger E. Genome-wide phage susceptibility analysis in Acinetobacter baumannii reveals capsule modulation strategies that determine phage infectivity. PLOS Pathogens. 2023;19.
137. Majkowska-Skrobek G, Markwitz P, Sosnowska E, Lood C, Lavigne R, Drulis-Kawa Z. The evolutionary trade-offs in phage-resistant Klebsiella pneumoniae entail cross-phage sensitization and loss of multidrug resistance. Environmental microbiology. 2021.
138. Guglielmotti D, Marcó M, Golowczyc M, Reinheimer J, Quiberoni A. Probiotic potential of Lactobacillus delbrueckii strains and their phage resistant mutants. International Dairy Journal. 2007;17:916-25.
139. Lo Curto A, Pitino I, Mandalari G, Dainty J, Faulks R, Wickham MSJ. Survival of probiotic lactobacilli in the upper gastrointestinal tract using an in vitro gastric model of digestion. Food microbiology. 2011;28 7:1359-66.
140. Gao H, Li, Sun W, McClements D, Cheng C, Zeng H, et al. Impact of encapsulation of probiotics in oil-in-water high internal phase emulsions on their thermostability and gastrointestinal survival. Food Hydrocolloids. 2021.
141. Suvarna S, Dsouza J, Ragavan M, Das N. Potential probiotic characterization and effect of encapsulation of probiotic yeast strains on survival in simulated gastrointestinal tract condition. Food Science and Biotechnology. 2018;27:745-53.
142. Zeashan M, Afzaal M, Saeed F, Ahmed A, Tufail T, Ahmed A, et al. Survival and behavior of free and encapsulated probiotic bacteria under simulated human gastrointestinal and technological conditions. Food Science & Nutrition. 2020;8:2419-26.
143. Gunzburg W, Aung M, Toa P, Ng S, Read E, Tan W, et al. Efficient Protection of Probiotics for Delivery to the Intestinal tract by Cellulose Sulphate Encapsulation. 2020.
144. Foster TJJNrm. Immune evasion by staphylococci. 2005;3(12):948-58.
145. Stummeyer K, Schwarzer D, Claus H, Vogel U, Gerardy-Schahn R, Mühlenhoff MJMm. Evolution of bacteriophages infecting encapsulated bacteria: lessons from Escherichia coli K1-specific phages. 2006;60(5):1123-35.
146. Pingoud A, Fuxreiter M, Pingoud V, Wende WJC, sciences ml. Type II restriction endonucleases: structure and mechanism. 2005;62:685-707.
147. Makarova KS, Grishin NV, Shabalina SA, Wolf YI, Koonin EVJBd. A putative RNA-interference-based immune system in prokaryotes: computational analysis of the predicted enzymatic machinery, functional analogies with eukaryotic RNAi, and hypothetical mechanisms of action. 2006;1:1-26.
148. Koonin EV, Makarova KSJPTotRSB. Origins and evolution of CRISPR-Cas systems. 2019;374(1772):20180087.
149. Lopatina A, Tal N, Sorek RJArov. Abortive infection: bacterial suicide as an antiviral immune strategy. 2020;7(1):371-84.
150. Vimon S, Kertsomboon T, Chirachanchai S, Angkanaporn K, Nuengjamnong CJCP. Matrices-charges of agar-alginate crosslinked microcapsules via o/w microemulsion: A non-spore forming probiotic bacteria encapsulation system for extensive viability. 2023;321:121302.
151. Kouamé KJE-P, Bora AFM, Li X, Sun Y, Hussain M, Liu L, et al. Recent Advances for Encapsulating Spore Forming and Non-Spore Forming Probiotic Bacteria: Applications in Functional Food Products. 2022.
152. Dalmasso M, Strain R, Neve H, Franz CM, Cousin FJ, Ross RP, et al. Three new Escherichia coli phages from the human gut show promising potential for phage therapy. 2016;11(6):e0156773.
153. Markwitz P, Olszak T, Gula G, Kowalska M, Arabski M, Drulis-Kawa ZJV. Emerging phage resistance in Pseudomonas aeruginosa PAO1 is accompanied by an enhanced heterogeneity and reduced virulence. 2021;13(7):1332.
154. Kaur S, Harjai K, Chhibber SJPo. In vivo assessment of phage and linezolid based implant coatings for treatment of methicillin resistant S. aureus (MRSA) mediated orthopaedic device related infections. 2016;11(6):e0157626.
155. Nakakido M, Tanaka N, Shimojo A, Miyamae N, Tsumoto KJPo. Development of a high-throughput method to screen novel antiviral materials. 2022;17(4):e0266474.
156. Jovanović M, Petrović M, Miočinović J, Zlatanović S, Laličić Petronijević J, Mitić-Ćulafić D, et al. Bioactivity and sensory properties of probiotic yogurt fortified with apple pomace flour. 2020;9(6):763.

157. Song M-W, Park J-Y, Lee H-S, Kim K-T, Paik H-DJA. Co-fermentation by Lactobacillus brevis B7 improves the antioxidant and immunomodulatory activities of hydroponic ginseng-fortified yogurt. 2021;10(9):1447.
158. Cordeiro BF, Alves JL, Belo GA, Oliveira ER, Braga MP, da Silva SH, et al. Therapeutic effects of probiotic minas frescal cheese on the attenuation of ulcerative colitis in a murine model. 2021;12:623920.
159. Chen L, Wu D, Schlundt J, Conway PLJFim. Development of a dairy-free fermented oat-based beverage with enhanced probiotic and bioactive properties. 2020;11:609734.
160. Gómez-Fernández AR, Faccinetto-Beltrán P, Orozco-Sánchez NE, Pérez-Carrillo E, Marín-Obispo LM, Hernández-Brenes C, et al. Sugar-free milk chocolate as a carrier of omega-3 polyunsaturated fatty acids and probiotics: A potential functional food for the diabetic population. 2021;10(8):1866.
161. Kumari VB C, Huligere SS, Alotaibi G, Al Mouslem AK, Bahauddin AA, Shivanandappa TB, et al. Antidiabetic activity of potential probiotics limosilactobacillus spp., levilactobacillus spp., and lacticaseibacillus spp. isolated from fermented sugarcane juice: a comprehensive in vitro and in silico study. 2023;15(8):1882.
162. D'Alessandro M, Parolin C, Bukvicki D, Siroli L, Vitali B, De Angelis M, et al. Probiotic and metabolic characterization of vaginal lactobacilli for a potential use in functional foods. 2021;9(4):833.
163. Vitellio P, Celano G, Bonfrate L, Gobbetti M, Portincasa P, De Angelis MJN. Effects of Bifidobacterium longum and Lactobacillus rhamnosus on gut microbiota in patients with lactose intolerance and persisting functional gastrointestinal symptoms: A randomised, double-blind, cross-over study. 2019;11(4):886.
164. Ashraf R, Shah N. Immune System Stimulation by Probiotic Microorganisms. Critical Reviews in Food Science and Nutrition. 2014;54:938-56.
165. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo J. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. Cells. 2023;12.
166. Galdeano M, Cazorla S, Dumit JML, Vélez E, Perdigón G. Beneficial Effects of Probiotic Consumption on the Immune System. Annals of Nutrition and Metabolism. 2019;74:115-24.
167. Xu H, Huang W, Hou Q, Kwok L-Y, Laga W, Wang Y, et al. Oral administration of compound probiotics improved canine feed intake, weight gain, immunity and intestinal microbiota. 2019;10:394673.
168. Stacey H, De Soir S, Jones J. The Safety and Efficacy of Phage Therapy: A Systematic Review of Clinical and Safety Trials. Antibiotics. 2022;11.
169. Fabijan AP, Iredell J, Danis-Wlodarczyk K, Kebriaei R, Abedon S. Translating phage therapy into the clinic: Recent accomplishments but continuing challenges. PLOS Biology. 2023;21.
170. Yang Q, Le S, Zhu T, Wu N. Regulations of phage therapy across the world. Frontiers in Microbiology. 2023;14.
171. Collins G, Dhiman P, Jie, Schlussel M, Archer L, Van Calster B, et al. Evaluation of clinical prediction models (part 1): from development to external validation. The BMJ. 2024;384.
172. Zbrozek A, Hebert J, Gogates G, Thorell R, Dell C, Molsen E, et al. Validation of electronic systems to collect patient-reported outcome (PRO) data-recommendations for clinical trial teams: report of the ISPOR ePRO systems validation good research practices task force. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013;16 4:480-9.
173. Toll D, Janssen K, Vergouwe Y, Moons K. Validation, updating and impact of clinical prediction rules: a review. Journal of clinical epidemiology. 2008;61 11:1085-94.
174. McMillen C, Doyle A, Claypool E. Validation as a clinical strategy. Journal of Social Work Practice. 2022;37:325-38.
175. Abedon S, Danis-Wlodarczyk K, Wozniak D. Phage Cocktail Development for Bacteriophage Therapy: Toward Improving Spectrum of Activity Breadth and Depth. Pharmaceuticals. 2021;14.
176. Kim MK, Suh G, Cullen G, Rodriguez SP, Dharmaraj T, Chang T. Bacteriophage therapy for multidrug-resistant infections: current technologies and therapeutic approaches. The Journal of Clinical Investigation. 2025;135.
177. Cha K, Oh HK, Jang JY, Jo Y, Kim WK, Ha GU, et al. Characterization of two novel bacteriophages infecting multidrug-resistant (MDR) Acinetobacter baumannii and evaluation of their therapeutic efficacy in vivo. 2018;9:696.
178. Shibu A, Kurup BM, Harikrishnan M, Boopendranath M. Impact of Climate Change on Hydrological Cycle, Ecosystem, Fisheries and Food Security. England. 2022.