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Phages and engineered lysins as an effective tool to combat Gram-negative foodborne pathogens

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Abstract

One of the biggest challenges faced by food producers is ensuring microbiological safety. Despite strict criteria for food products, foodborne diseases are a global problem and pose a real risk to consumers. Therefore, it is necessary to identify new and more effective methods for eliminating pathogens from food and the food processing environment. According to the European Food Safety Authority (EFSA), the most common foodborne diseases are caused by *Campylobacter*, *Salmonella*, *Yersinia*, *Escherichia coli*, and *Listeria*. Out of the five listed, four are Gram-negative bacteria. Our review focuses on the use of bacteriophages, which are ubiquitous bacterial viruses, and bacteriophage endolysins to eliminate Gram-negative pathogens. Endolysins cleave specific bonds within the peptidoglycan (PG) of the bacterial cell, causing the cell to burst. Single phages or phage cocktails, which are, in some instances, commercially available products, eliminate pathogenic bacteria in livestock and various food matrices. Endolysins have matured as the most advanced class of antibacterial agents in the clinical sector, but their use in food protection is highly unexplored. Advanced molecular engineering techniques, different formulations, protein encapsulation, and the addition of outer membrane (OM) permeabilization agents enhance the activity of lysins against Gram-negative pathogens. This creates space for groundbreaking research on the use of lysins in the food sector.

KEYWORDS
antimicrobial, bacteriophage, endolysin, engineered lysin, food safety, Gram-negative foodborne pathogen, lysin

1 | INTRODUCTION

Microbiological food safety is one of the main concerns of food producers; specifically, food producers must ensure that food products are free from pathogens, their toxins, persisters, and viruses and that certain substances do not exceed the allowable doses based on standards and regulations (Ricci et al., 2017). Despite advanced tools such as cleaning-in-place (CIP) and disinfection protocols and the availability of a broad spectrum of antimicrobial substances, foodborne diseases remain a global problem even in the 21st century (Bintsis, 2017).

According to World Health Organization (WHO) data, every year, 600 million people in the world fall ill after eating contaminated food, and 420,000 of these people die (WHO, 2022). The European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC) and WHO report that the most common foodborne pathogens are Gram-negative pathogens, mainly *Campylobacter*, *Salmonella*, Shiga toxin-producing *Escherichia coli* (STEC), and *Yersinia* besides less prevalent but serious foodborne Gram-positive pathogens such as *Listeria monocytogenes* and *Staphylococcus aureus* (EFSA, 2021; WHO, 2022). A factor exacerbating the scale of the problem is the global antimicrobial resistance crisis, which affects not only the medical sector but also the food sector (Hernando-Amado et al., 2019; Sabtu et al., 2015). Therefore, food producers seek new and more effective antibacterial agents to reduce the occurrence of foodborne pathogens and counteract the problem of antibiotic resistance.

A recent trend in this field has focused on the use of phages and phage-derived lysins (Xu 2021a). Phages are viruses that infect bacteria. To lyse an infected cell at the end of the phage replication cycle, phage-derived lysins are produced that degrade the peptidoglycan (PG) layer of the bacterial cell wall (Oliveira et al., 2018). Both phages and lysins have been widely investigated as antibacterial agents (Schmelcher et al., 2012; Xu 2021a). Gram-negative bacteria are generally more resistant to antimicrobial substances than Gram-positive bacteria due to their outer membrane (OM) (Breijyeh et al., 2020). The combined hydrophilic and hydrophobic properties of the OM render the OM largely impermeable to antibacterial compounds. Only smaller antibiotics (β-lactams, tetracycline, chloramphenicol, and fluoroquinolones) can pass through the OM either through embedded porins, exploiting the Tol–Pal system (e.g., colicins), or by interference with the stabilizing forces of the OM (e.g., colistin) (Delcour, 2009; Nikaido, 2003). Importantly, phage-derived lysins are generally too large to pass through the OM (Gutiérrez & Briers, 2021). This review therefore focuses on the potential of phages and phage-encoded lysins in combating Gram-negative foodborne pathogens. We present the current trends in improving the activity of lysins against Gram-negative bacteria, underscoring the possibilities associated with molecular engineering strategies. Furthermore, we discuss the gap in knowledge related to evaluating these novel enzyme-based antibacterials against foodborne pathogens, in specific food matrices, against biofilms and under food processing and storage conditions, highlighting future research directions.

2 | METHODOLOGY

A literature search of PubMed, Web of Knowledge and Scopus was performed, searching all databases using the terms "bacteriophages/phages in food," "bacteriophages/phages and food safety," "bacteriophages/phages and foodborne pathogens," "endolysins/lysins in food," "endolysins/lysins in food protection," and "endolysins/lysins and foodborne pathogens." Based on the title and abstract, we included scientific articles published online until December 2022. Since (i) the number of reports on the use of bacteriophages in the food sector far outnumber those on the use of lysins and (ii) Gram-negative bacteria are the most common cause of foodborne outbreaks, the scientific articles selected for this review had to meet the following criteria. They had to be written in English, published in the last 5 years if they reported on phages and in the last 10 years if they reported on endolysins/lysins, and focused on the role of phages/lysins in food protection and food safety and in targeting Gram-negative bacteria. Articles written in a language other than English, focusing on the elimination of Gram-positive bacteria, Gram-positive foodborne pathogens, and clinical Gram-negative bacteria were excluded.

3 | PHAGES USED IN THE FOOD INDUSTRY

Phages are the most abundant biological entities on earth; notably, there are an estimated 10^{31} phages (García et al., 2010a). They are viruses targeting bacteria, generally have a narrow host range, and are usually not capable of crossing genus and species barriers (Fong et al., 2021; Gray et al., 2018). Nevertheless, a diversity of phages that are also able to infect bacterial isolates across the bacterial species or genus level have been reported, for example, polyvalent phages SS3e (Kim et al., 2018) or JHP (Khawaja et al., 2016). High specificity distinguishes bacteriophages from commonly used antibiotics, which, in addition to pathogens, can kill natural animal or human microbiota (Loc-Carrillo & Abedon, 2011). Generally, phages can be differentiated based on morphology, the presence of nucleic acids, and the lytic or lysogenic replication cycle (Kasman & Porter, 2021).

Research on the therapeutic usage of phages began in the 1920s, but due to the discovery of penicillin and the development of antibiotic therapy, the clinical application of phages was largely abandoned (Murray et al., 2021).

Nevertheless, research on phage therapy has successfully continued in some Eastern European countries, such as Poland, Georgia, and Russia (García et al., 2008; Mariawienhold et al., 2019). Phage therapy has been applied in several human case studies, for instance, in the treatment of sepsis and meningitis, and the given advantages of using bacteriophages include an increase in number over the course of treatment, low inherent toxicities, and the ability to destroy bacteria organized into biofilms (Paule et al., 2018; Pirnay & Kutter, 2021; Sulakvelidze et al., 2001; van Nieuwenhuyse et al., 2022). Moreover, as mentioned above, the greatest advantage is the high specificity of most phages for a particular host cell, which, with the exceptions of polyvalent phages, promotes the elimination of a specific bacterium without destroying the surrounding microbiome (Połaska & Sokołowska, 2019). Thus, phages are an interesting tool for pathogen elimination in the fermentation industry, as they do not destroy the starter or autochthonous microorganisms that shape the organoleptic features of the product (Kawacka et al., 2020). Years of phage research have led to the widespread use of phages in the food industry (Table 1), and many preparations are currently commercially available to eliminate Gram-negative foodborne pathogens (Table 2) (Moye et al., 2018; Vikram et al., 2022).

3.1 | *Campylobacter jejuni*

Camphylobacter jejuni is the etiological agent of campylobacteriosis, a form of human gastroenteritis that is most often diagnosed as a result of consuming contaminated poultry (Thornval & Hoorfar, 2021). The symptoms appear 2–5 days after eating contaminated food and include diarrhea, nausea, vomiting, fever, and stomach cramps (Facciolà et al., 2017). Since *C. jejuni* is mainly transmitted by poultry, the effectiveness of phages against this pathogen has been investigated, particularly in broiler chickens (D'angelantonio et al., 2021; Richards et al., 2019) and on chicken farms (Chinivasagam et al., 2020) (Table 1). The first such study assessed the effect of a phage cocktail on eliminating *C. jejuni* HPC5 from broiler chickens and the effect of phage treatment on altering the chicken microbiome, which is an important outcome of the system-wide effects of phage therapy (Richards et al., 2019). Broiler chickens were orally infected with 10^7 CFU of *C. jejuni* HPC5 in 1 mL of PBS (Phosphate Buffered Saline) and were treated with 10^7 PFU/mL of a phage cocktail of CP20 and CP30A; the effects on *C. jejuni* HPC5 cell reduction and alterations in the chicken microbiota were assessed. The highest reduction in *C. jejuni* HPC5 was reported 2 days after phage treatment, and the reduction level was estimated at 2.4 log CFU/g in cecal contents. This was a significant difference compared to chickens colonized with *C. jejuni* but not treated with the phage cocktail. Moreover, the phages acted selectively to reduce the number of *C. jejuni* without affecting the normal chicken microbiota (Richards et al., 2019). In another study, D'angelantonio et al. (2021) evaluated the efficiency of two phages, Φ 16-izsam and Φ 7-izsam, against *C. jejuni* infection in broilers. The phages were administered on the 38th and 39th days of rearing as follows: first Φ 16-izsam and then Φ 7-izsam in a dose corresponding to a multiplicity of infection (MOI) of 0.1 and 1.0, depending on the group (the same amount at both time points). After slaughter, there was a statistically significant reduction in the number of *C. jejuni* in cecal contents. The reduction levels were 1 and 2 log CFU/g for MOIs of 0.1 and 1.0, respectively, compared to the control. The results indicated a dose-dependent effectiveness of phage therapy against *C. jejuni* infection in chickens (D'angelantonio et al., 2021). In turn, Chinivasagam et al. (2020) tested the usefulness of phages to control *C. jejuni* on Australian commercial broiler farms. Phage therapy was applied to birds from farms where no phages against *Campylobacter* were detected a week before the planned experiment, and the birds were monitored from the farm to the processing plant. A decrease in the concentration of *Campylobacter* was observed in the range of 1–3 log CFU/g on Farm A, where the birds underwent phage therapy, but the presence of single cases with a low phage titer and high *Campylobacter* content were also found. The results suggested that longer phage treatment periods may be required to ensure efficient phage replication for effective biocontrol in vivo. In addition, it was observed that *Campylobacter*-specific phages on Farm B also appeared in the control group, resulting in a *Campylobacter* reduction of 1.7 log CFU/g, indicating the rapid spread of infiltrating phages throughout the flock. Nevertheless, the obtained results indicated the efficacy of phage therapy against *Campylobacter* infection on poultry farms (Chinivasagam et al., 2020).

3.2 | *Salmonella* spp.

Salmonella causes approximately 93.8 million cases of foodborne diseases globally each year, with 155,000 deaths (Gong et al., 2022). The main source of *Salmonella* outbreaks is contaminated food such as eggs, pork, beef, chicken, fruits, vegetables, sprouts, and processed foods (including peanut butter, chicken nuggets, or frozen pot pies) (Gómez-Aldapa et al., 2012). Symptoms of *Salmonella* infection (salmonellosis) appear approximately 6 h to 6 days after eating contaminated food, and the main symptoms of salmonellosis are stomach cramps, diarrhea, and fever (Giannella, 1996).

TABLE 1 Phages tested against Gram-negative foodborne pathogens in food matrices and their proposed use in food.

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
Campylobacter jejuni HPC5	Phage cocktail of *Campylobacter* phages CP20 and CP30A; single dose of 7 log PFU/mL	Commercial broiler chicken excreta	Combating *C. jejuni* in chickens ileum, ceca, and colon without affecting the wider microbiota, the reduction level depends on the section of the digestive tract, reduction of 2.4 log units in cecal content (pre-harvest)	(Richards et al., 2019)
C. jejuni, Campylobacter coli	Phage cocktail of 19 candidates (out of 128 phages screened); 3 mL of 7 log PFU/mL	Cecal contents, litter, carcass rinses, and soil from Queensland broiler chicken farms and pig effluent	Combating *Campylobacter* strains (241 representative isolates) from commercial broiler chicken farms in Australia (reduction level of 1–3 log CFU/g on Farm A and 1.7 log CFU/g on Farm B, but also in the control group on Farm B) (pre-harvest)	(Chinivasagam et al., 2020)
C. jejuni	Two phages (Φ 16-izsam and Φ 7-izsam; 7 log PFU/mL (MOI 0.1) and 8 log PFU/mL (MOI 1.0)	Cloacal swabs, fresh feces, boot socks and water samples from the cooling systems of poultry farms	Reduction of 1–2 log CFU/g in C. *jejuni* cells in broiler chickens (pre-harvest)	(D'angelantonio et al., 2021)
Yersinia enterocolitica	Two phages (fHe-Yen3-01 and fHe-Yen9-01; 1.77×10^8 PFU/g—raw pork; 1.98×10^8 PFU/mL—milk; 1.82×10^8 PFU/g—RTE pork	Sewage samples in Finland	Reductions of 1–3 log units from the original levels of 2–4 $\times 10^3$ CFU/g or mL of *Yersinia enterocolitica* on raw pork, ready-to-eat (RTE) pork, and milk (post-harvest)	(Jun et al., 2018)
S. Enteritidis	SE07; 11–12 log PFU/mL	Retail meat samples	Reduction of bacterial growth (~2 log units) in fruit juice, fresh eggs, beef, and chicken meat (post-harvest)	(Thung et al., 2017)
Salmonella	Three-phage cocktail (alginate/$CaCO_3$ encapsulated phages UAB_Phi20, UAB_Phi78, UAB_Phi87; 11 log PFU/mL)	Chicken and pig farms	Significantly greater reductions in the *Salmonella* concentration in the ceca of broiler chickens obtained with a cocktail of alginate/$CaCO_3$-encapsulated phages than that achieved with phages alone (from day 8 until the end of the experiment at day 15) (pre-harvest)	(Colom et al., 2017)
Salmonella strains	Phages S16 and FO1a	PhageGuard S™ (formerly Salmonelex™)	Reduction of *Salmonella* cells in ground chicken, reduction level depends on the water source used to dilutions, susceptibility of strains to the phage and time after ~7log PFU/cm^2 application (post-harvest)	(Grant et al., 2017)
			Reduction of cells in ground beef (~1 log units, higher reduction after phage treatment supported with ultraviolet light, ~2 log units) after 9 log PFU/mL application (post-harvest)	(Yeh et al., 2018)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
			Reduction > 1 log of *Salmonella* cells on poultry products after 1 and 2×10^7 PFU/cm^2 application (post-harvest)	(Hagens et al., 2018)
S. Enteritidis and *S.* Typhimurium	Five-phage cocktail; 30 μL of 3 $\times 10^8$ PFU/mL	Chicken skin and gizzard samples	Reduction of bacterial cells in row chicken meat, *S.* Enteritidis, and *S.* Typhimurium reductions of 1.41 and 1.86 log CFU/piece, and 3.06 and 2.21 log units at 8 and 25°C, respectively (post-harvest)	(Duc et al., 2018)
S. Typhimurium	LPST10; MOI 1, 10 and 100	Poultry house, sewage near a river, farm ditch	Reduction (0.92−5.12 log CFU/sample) of *Salmonella* cells in milk, sausage, and lettuce (post-harvest)	(Huang et al., 2018)
Salmonella	Six-phage cocktail; 8 log PFU/mL	SalmoFresh™	Reduction of *Salmonella* cells on lettuce and sprouts (higher reduction levels at 2 and 10°C than at 25°C) (post-harvest)	(Zhang et al., 2019)
Salmonella	Six-phage cocktail; 8 log PFU/mL	SalmoFREE®	Reduction of *Salmonella* cells in broiler chickens farms, reduction level depends on experimental design; nevertheless, the efficiency of SamoFREE® against *Salmonella* outbreaks was confirmed (pre-harvest)	(Clavijo et al., 2019)
S. Typhimurium	Three-phage cocktail (phages BSPM4, BSP101, and BSP22A); MOI 1000 and 10,000	Environmental samples	Reduction of 2.8−3.9 log CFU/cm^2 on iceberg lettuce and 2.5−2.8 log CFU/cm^2 on cucumber after 4 h at 25°C at an MOI of 10^4; 4.7−5.5 log CFU/cm^2 reduction of viable cell number on iceberg lettuce and 4.8−5.8 log CFU/cm^2 reduction on cucumber after 12 h at 25°C (post-harvest)	(Bai et al., 2019a)
Salmonella	Three-phage cocktail (phages LPSTLL, LPST94, and LPST153); MOI 1000—to reach a final titer of 6 log PFU/mL and MOI 10,000—7 log PFU/mL in milk or 6−7 PFU/cm^2 on surface of the chicken breast samples	Environmental water samples	Reduction of bacterial cells (below detectable limits) in milk and chicken breast; reduction of 72 h biofilm on a 96-well microplate and stainless steel surface; >5.23 log reduction in *Salmonella* viable cells (post-harvest)	(Islam et al., 2019)
S. Enteritidis	Four-phage cocktail; MOI of 10^4, 10^5, and 10^6	River proximate to a duck farm	Significant reduction of *Salmonella* cells in row chicken breast meat stored 4°C for 7 days (post-harvest)	(Kim et al., 2020)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
S. Enteritidis	Phages PSE1, PSE2, PSE3, PSE4, and PSE5; MOI 0.01	Poultry slaughterhouse wastewater	Reduction of *Salmonella* cells by 2×10^6 CFU/mL in raw eggs (post-harvest)	(Sonalika et al., 2020)
S. Enteritidis	Three wild-type bacteriophages CNPSA 1, CNPSA 3, and CNPSA 4; 9 log PFU/mL	Free-range chickens of southern Brazil	Reduction (1.08 log CFU/g) of *S.* Enteritidis in broiler chickens (pre-harvest)	(Vaz et al., 2020)
Salmonella enterica	Phage cocktail; 2.5×10^8 PFU/cm^2	Various source (pretreated sludge, virus collection)	Reduction by 1–4 log CFU/cm^2 of bacterial cells on lettuce leaves and cantaloupe flesh. The cocktail was not effective against *Salmonella* Newport S195 on both fresh produce commodities (post-harvest)	(Wong et al., 2020)
S. Enteritidis	LSE7621; MOI 1 and 100	Swage samples from poultry farms	Bactericidal activity on lettuce (reduction of 1.02 and 0.86 log CFU/mL) and tofu (1.86 and 3.55 log CFU/mL) under MOI 1 and 100, respectively (post-harvest)	(Liu et al., 2020)
S. Enteritidis	Three phages UPWr_S1, UPWr_S3, and UPWr_S4; three-phage cocktail UPWr_S134; ~7 log PFU/mL was added to water in drinkers	Feces, litter, and manure from poultry farms, drainage ditches, and treatment plants	Reduction of biofilm on a 96-well microplate (up to 87%) and stainless steel surface (up to 98%). Reduction of *S.* Enteritidis cell number from the poultry drinker surface (pre-harvest)	(Korzeniowski et al., 2022)
Salmonella strains	LPST94; MOI 1000 and 10,000	Environmental water Samples	Reduction of *Salmonella* cells 0.84–3.0 log CFU/mL in milk, and apple juice, and below the level of detection on chicken breast and lettuce; more effective at 4°C than 25°C (post-harvest)	(Islam et al., 2020b)
Salmonella strains	D10; 100 μL of 10^8 or 10^9 PFU/mL	Environmental resources	Inhibition in *Salmonella* growth in liquid egg white and egg yolk at 4 and 25°C (post-harvest)	(Li et al., 2021b)
S. Typhimurium	LPST153; MOI 1000 and 10,000, 7 log and 8 log PFU/mL was applied to the *Salmonella* biofilm	Water samples, lakes in Wuhan, China	Reduction of *Salmonella* cells in milk and sausage (0.7–3.3 log units); reduction of existing biofilm formed in 96-well microtiter plate (post-harvest)	(Islam et al., 2020a)
S. Typhimurium ATCC 13311	LPSEYT; 6 log PFU/mL (MOI 1000) and 7 log PFU/mL (MOI 10,000)	Water samples, Wuhan, China	Reduction of *Salmonella* cells (2.07–4.22 log units) in milk and lettuce at both 4 and 25°C (post-harvest)	(Yan et al., 2020)
Salmonella strains	T156; MOI 1000 and 10,000	Local wastewater (Wuhan)	Inhibition of *Salmonella* growth in artificially contaminated milk and lettuce (efficacy of 57.93% and 55.47%, respectively) at 4°C (post-harvest)	(Li et al., 2021a)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
S. Enteritidis and *S.* Typhimurium	Pu20; MOI 1000 and 10,000	Sewage samples	Reduction of *Salmonella* cells in liquid eggs (egg white and yolk); higher effect at 4°C than 25°C, the maximum antibacterial efficiency was 91.30% and 92.40%, respectively (post-harvest)	(Zhang et al., 2021b)
Salmonella	S1; 4.9×10^9 PFU	Wastewater	Reduction of *Salmonella* cells in chicken model of infection, reduction level depends on time after treatment (pre-harvest)	(Gomez-Garcia et al., 2021)
Salmonella strains Including *S.* Enteritidis, *S.* Typhimurium, and *Staphylococcus gallinarum*	Four-phage cocktail (8sent1748, 8sent65, 3sent1, and 5sent1); 3×10^7 PFU/g of feed or 2×10^6 PFU/bird/day	Bafasal™	Reduction of *Salmonella* (by more than 16 times, Δlog10 (CFU/g) = 1.21 log) content in caeca of birds infected with *S.* Enteritidis. Activity against *S.* Enteritidis, *S.* Typhimurium, and *S. gallinarum* in spot tests (pre-harvest)	(Wójcik et al., 2020)
S. Typhimurium	Two phages (vB_SenM-2 and vB-Sen-TO17; 2×10^9 PFU/mL	Chicken feces	Elimination of *Salmonella* cells in chicken model of infection, the most efficient was treatment started 1 day after infection (pre-harvest)	(Kosznik-Kwasnicka et al., 2022)
S. Typhimurium	Two-phage cocktail (SPFM10 and SPFM14); ~4 log PFU/g	Food processing plant (SPFM10) and pig feces (SPFM14)	Reduction of *Salmonella* colonization in different gut compartments. *Salmonella* counts were reduced by on average 1 log CFU/g in stomach tissue, colon, and cecum, and 2 log CFU/g in duodenum tissue of piglets (pre-harvest)	(Thanki et al., 2022)
S. Enteritidis, *S.* Typhimurium, and *E. coli* O157:H7	PS5; 100 μL of 10 log PFU/mL	Chicken products	Reduction of bacterial cells (≥1.2 log CFU/piece or mL) in row chicken skin, row beef, lettuce, whole fat pasteurized milk, and liquid egg. For example, in milk, phage PS5 reduced the viable counts of *E. coli* O157:H7 to under detection limit (<10 CFU/mL) (post-harvest)	(Duc et al., 2020)
E. coli ATCC 13706	Phages phT4A and ECA2 and two-phage cocktail (phT4A/ECA2); 5 PFU/mL (MOI 1) and 7 PFU/mL (MOI 100)	Sewage network of Aveiro, Portugal	Reduction of bacterial cells (~2.0 log CFU/g for artificially and ~0.7 log CFU/g for naturally contaminated cockles) (pre/post-harvest)	(Pereira et al., 2017)
Shiga-toxin-producing *Escherichia coli* (STEC)	Four-phage cocktail; 8 log PFU/mL	Commercial prototype	Reduction of *E. coli* STEC O157, O121, and O103 (0.4 to 0.7 log CFU/cm^2) on beef cattle hide pieces (post-harvest)	(Tolen et al., 2018)
Shiga-toxin-producing *E. coli* (STEC) O157:H7	PE37; 20 μL of 5×10^7 PFU/mL	Bovine intestine	Significant reductions in the viable cells of STEC in artificially contaminated beef stored at 25°C (2.3 log CFU/piece) and 8°C (0.9 log CFU/piece) (post-harvest)	(Son et al., 2018)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
Enteropathogenic *E. coli* (EPEC) and Shiga-toxin-producing *E. coli* (STEC)	Six-phage cocktail; 8–9 log PFU/mL	Stool samples of patients with diarrhea	Reduction of both EPEC and STEC (reduction level depends on temperature) in meat and milk stored at 4, 24, and 37°C (post-harvest)	(Tomat et al., 2018)
Shiga-toxin-producing *E. coli* (STEC) O157:H7	vB_EcoM-ECP26; 6 log PFU/mL	Sewage sample from Seongnam Water Reclamation Center (Gyeonggi, South Korea)	Reduction of STEC on romaine lettuce to undetectable levels 5 days after phage exposure (pre-harvest)	(Park et al., 2020)
E. coli O157:H7	Phage cocktail; 5×10^6 and 1×10^7 PFU/g	EcoShield PX™	Significant reductions in *E. coli* O157:H7 levels (up to 97%) in beef chuck roast, ground beef, chicken breast, cooked chicken, salmon, cheese, cantaloupe, and romaine lettuce (post-harvest)	(Vikram et al., 2020b)
Shiga-toxin producing *Escherichia coli* (STEC)	Three-phage cocktail (FM10, DP16, and DP19); MOI 0.1, 1.0, and 10	Sewage, feces, bedding material of cattle	Reduction of *E. coli* cells on the cucumber surface stored at 25°C (1.97–2.01 log CFU/g) and 4°C (1.16–2.01 log CFU/g) for 24 h (post-harvest)	(Mangieri et al., 2020)
E. coli O157:H7	Phages EP75 and EP335; 8 log PFU/mL	PhageGuard E™	Reduction of *E. coli* cells in Beef Rose Meat kept under vacuum and aerobic conditions; under both conditions phage cocktail reduced *E. coli* O157:H7 in beef by approximately 1.4 log (post-harvest)	(Shebs et al., 2020)
E. coli O157:H7	JN01; 100 μL or 200 μL of 9 log PFU/mL	Wastewater	Reduction of *E. coli* O157:H7 cells in UHT milk (2.96 CFU/mL in the control group after 3 days storage at 4°C, 1.5 log CFU/mL in phage-treated sample at the beginning of storage, and undetectable levels within 1–3 days of storage; raw beef (the numbers of *E. coli* O157: H7 in the phage-treated samples decreased to 2.5, 2.3, 1.7, 1.5, and 1.8 log CFU/cm^2 after stored at 4°C for 0, 1, 3, 5, and 7 days) (post-harvest)	(Li et al., 2021c)
E. coli O157:H7 *S.* Typhimurium	EscoHU1; 50 μL of 2×10^9 PFU/mL (milk) or 100 μL of 2×10^9 PFU/cm^2 (beef)	River water in Hokkaido, Japan; *E. coli* O157:H7 RIMD 0509939 is the host strain	EscoHU1 suppressed the growth of *E. coli* O157:H7 in milk (1.2 log CFU/mL reduction at 72 h), and beef *E. coli* 1.7 log CFU/cm^2 reduction at 3 h in phage-treated samples; slight decrease (0.2 log CFU/cm^2) of *S.* Typhimurium in the beef stored for 72 h; the antimicrobial effect of phage on *S.* Typhimurium in milk was limited (post-harvest)	(Yamaki et al., 2022)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in Food	Reference
Shiga-toxin producing *E. coli* O26:H11	vB_EcoM_VR26 (VR26); 8 log PFU/cm^2	Isolated in Lithuania using *E. coli* MH1 strain as a host	Reduction of *E. coli* O26:H11 by approximately 2 log CFU/piece on lettuce at 4, 8, and 22°C (post-harvest)	(Zajančkauskaitė et al., 2021)
Pseudomonas lactis	Phage from raw cow's milk; 6×10^7 PFU	Raw cow's milk	Reduction (1000-fold compared to control) of viable bacterial cell in both skim and whole milk (post-harvest)	(Tanaka et al., 2018)
Shigella sonnei	Five-phage cocktail; 5–7 log PFU/g	ShigaShield™	Reduction of *Shigella* cells (>1 log units) in deli meat, smoked salmon, pre-cooked chicken, lettuce, and yogurt except for the lowest phage dose (9×10^5 PFU/g) on melon where reduction was only 0.25 log (post-harvest)	(Soffer et al., 2017)
Shigella flexneri	vB_SflS-ISF001; 8 log PFU/g	Wastewater	Reduction in the count of viable *S. flexneri* PTCC 1234 cells by ~2 logs in raw and cooked chicken breast 24 h after host inoculation; after 48 and 72 h, the numbers of viable *S. flexneri* cells were <100 CFU/g (post-harvest)	(Shahin & Bouzari, 2017)
Target bacteria	**Phage and dosage**	**Phage source**	**Applications in food**	**Reference**
Campylobacter jejuni HPC5	Phage cocktail of *Campylobacter* phages CP20 and CP30A; single dose of 7 log PFU/mL	Commercial broiler chicken excreta	Combating *C. jejuni* in chickens ileum, ceca, and colon without affecting the wider microbiota, the reduction level depends on the section of the digestive tract, reduction of 2.4 log units in cecal content (pre-harvest)	(Richards et al., 2019)
C. jejuni, Campylobacter coli	Phage cocktail of 19 candidates (out of 128 phages screened); 3 mL of 7 log PFU/mL	Cecal contents, litter, carcass rinses, and soil from Queensland broiler chicken farms and pig effluent	Combating *Campylobacter* strains (241 representative isolates) from commercial broiler chicken farms in Australia (reduction level of 1–3 log CFU/g on Farm A and 1.7 log CFU/g on Farm B, but also in the control group on Farm B), (pre-harvest)	(Chinivasagam et al., 2020)
C. jejuni	Two phages (Φ 16-izsam and Φ 7-izsam; 7 log PFU/mL (MOI 0.1) and 8 log PFU/mL (MOI 1.0)	Cloacal swabs, fresh feces, boot socks, and water samples from the cooling systems of poultry farms	Reduction of 1–2 log CFU/g in C. *jejuni* cells in broiler chickens (pre-harvest)	(D'angelantonio et al., 2021)
Yersinia enterocolitica	Two phages (fHe-Yen3-01 and fHe-Yen9-01; 1.77×10^8 PFU/g—raw pork; 1.98×10^8 PFU/mL—milk; 1.82×10^8 PFU/g—RTE pork	Sewage samples in Finland	Reductions of 1–3 log units from the original levels of $2–4 \times 10^3$ CFU/g or mL of *Yersinia enterocolitica* on raw pork, ready-to-eat (RTE) pork, and milk (post-harvest)	(Jun et al., 2018)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in food	Reference
S. Enteritidis	SE07; 11–12 log PFU/mL	Retail meat samples	Reduction of bacterial growth (~2 log units) in fruit juice, fresh eggs, beef, and chicken meat (post-harvest)	(Thung et al., 2017)
Salmonella	Three-phage cocktail (alginate/$CaCO_3$-encapsulated phages UAB_Phi20, UAB_Phi78, UAB_Phi87; 11 log PFU/mL)	Chicken and pig farms	Significantly greater reductions in the *Salmonella* concentration in the ceca of broiler chickens obtained with a cocktail of alginate/$CaCO_3$-encapsulated phages than that achieved with phages alone (from day 8 until the end of the experiment at day 15) (pre-harvest)	(Colom et al., 2017)
Salmonella strains	Phages S16 and FO1a	PhageGuard S™ (formerly Salmonelex™)	Reduction of *Salmonella* cells in ground chicken, reduction level depends on the water source used to dilutions, susceptibility of strains to the phage and time after ~7 log PFU/cm^2 application (post-harvest)	(Grant et al., 2017)
			Reduction of cells in ground beef (~1 log units, higher reduction after phage treatment supported with ultraviolet light, ~2 log units) after 9 log PFU/mL application (post-harvest)	(Yeh et al., 2018)
			Reduction >1 log of *Salmonella* cells on poultry products after 1 and 2×10^7 PFU/cm^2 application (post-harvest)	(Hagens et al., 2018)
S. Enteritidis and *S.* Typhimurium	Five-phage cocktail; 30 μL of 3×10^8 PFU/mL	Chicken skin and gizzard samples	Reduction of bacterial cells in row chicken meat, *S.* Enteritidis, and *S.* Typhimurium reductions of 1.41 and 1.86 log CFU/piece, and 3.06 and 2.21 log units at 8 and 25°C, respectively (post-harvest)	(Duc et al., 2018)
S. Typhimurium	LPST10; MOI 1, 10 and 100	Poultry house, sewage near a river, farm ditch	Reduction (0.92–5.12 log CFU/sample) of *Salmonella* cells in milk, sausage, and lettuce (post-harvest)	(Huang et al., 2018)
Salmonella	Six-phage cocktail; 8 log PFU/mL	SalmoFresh™	Reduction of *Salmonella* cells on lettuce and sprouts (higher reduction levels at 2 and 10°C than at 25°C) (post-harvest)	(Zhang et al., 2019)
Salmonella	Six-phage cocktail; 8 log PFU/mL	SalmoFREE®	Reduction of *Salmonella* cells in broiler chickens farms, reduction level depends on experimental design; nevertheless, the efficiency of SamoFREE® against *Salmonella* outbreaks was confirmed (pre-harvest)	(Clavijo et al., 2019)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in food	Reference
S. Typhimurium	Three-phage cocktail (phages BSPM4, BSP101, and BSP22A); MOI 1000 and 10,000	Environmental samples	Reduction of 2.8–3.9 log CFU/cm^2 on iceberg lettuce and 2.5–2.8 log CFU/cm^2 on cucumber after 4 h at 25°C at an MOI of 10^4; 4.7–5.5 log CFU/cm^2 reduction of viable cell number on iceberg lettuce and 4.8–5.8 log CFU/cm^2 reduction on cucumber after 12 h at 25°C (post-harvest)	(Bai et al., 2019a)
Salmonella	Three-phage cocktail (phages LPSTLL, LPST94, and LPST153); MOI 1000—to reach a final titer of 6 log PFU/mL and MOI 10,000—7 log PFU/mL in milk or 6–7 PFU/cm^2 on surface of the chicken breast samples	Environmental water samples	Reduction of bacterial cells (below detectable limits) in milk and chicken breast; reduction of 72 h biofilm on a 96-well microplate and stainless steel surface; >5.23 log reduction in *Salmonella* viable cells (post-harvest)	(Islam et al., 2019)
S. Enteritidis	Four-phage cocktail; MOI of 10^4, 10^5, and 10^6	River proximate to a duck farm	Significant reduction of *Salmonella* cells in row chicken breast meat stored 4°C for 7 days (post-harvest)	(Kim et al., 2020)
S. Enteritidis	Phages PSE1, PSE2, PSE3, PSE4, and PSE5; MOI 0.01	Poultry slaughterhouse wastewater	Reduction of *Salmonella* cells by 2×10^6 CFU/mL in raw eggs (post-harvest)	(Sonalika et al., 2020)
S. Enteritidis	Three wild-type bacteriophages CNPSA 1, CNPSA 3, and CNPSA 4; 9 log PFU/mL	Free-range chickens of southern Brazil	Reduction (1.08 log CFU/g) of *S.* Enteritidis in broiler chickens (pre-harvest)	(Vaz et al., 2020)
Salmonella enterica	Phage cocktail; 2.5×10^8 PFU/cm^2	Various source (pretreated sludge, virus collection)	Reduction by 1–4 log CFU/cm^2 of bacterial cells on lettuce leaves and cantaloupe flesh. The cocktail was not effective against *Salmonella* Newport S195 on both fresh produce commodities (post-harvest)	(Wong et al., 2020)
S. Enteritidis	LSE7621; MOI 1 and 100	Swage samples from poultry farms	Bactericidal activity on lettuce (reduction of 1.02 and 0.86 log CFU/mL) and tofu (1.86 and 3.55 log CFU/mL) under MOI 1 and 100, respectively (post-harvest)	(Liu et al., 2020)
S. Enteritidis	Three phages UPWr_S1, UPWr_S3, and UPWr_S4; three-phage cocktail UPWr_S134; ~7 log PFU/mL was added to water in drinkers	Feces, litter, and manure from poultry farms, drainage ditches and treatment plants	Reduction of biofilm on a 96-well microplate (up to 87%) and stainless steel surface (up to 98%). Reduction of *S.* Enteritidis cell number from the poultry drinker surface (pre-harvest)	(Korzeniowski et al., 2022)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in food	Reference
Salmonella strains	LPST94; MOI 1000 and 10,000	Environmental water samples	Reduction of *Salmonella* cells 0.84–3.0 log CFU/mL in milk, and apple juice, and below the level of detection on chicken breast and lettuce; more effective at 4°C than 25°C (post-harvest)	(Islam et al., 2020b)
Salmonella strains	D10; 100 μL of 10^8 or 10^9 PFU/mL	Environmental resources	Inhibition in *Salmonella* growth in liquid egg white and egg yolk at 4 and 25°C (post-harvest)	(Li et al., 2021b)
S. Typhimurium	LPST153; MOI 1000 and 10,000, 7 log and 8 log PFU/mL was applied to the *Salmonella* biofilm	Water samples, lakes in Wuhan, China	Reduction of *Salmonella* cells in milk and sausage (0.7–3.3 log units); reduction of existing biofilm formed in 96-well microtiter plate (post-harvest)	(Islam et al., 2020a)
S. Typhimurium ATCC 13311	LPSEYT; 6 log PFU/mL (MOI 1000) and 7 log PFU/mL (MOI 10,000)	Water samples, Wuhan, China	Reduction of *Salmonella* cells (2.07–4.22 log units) in milk and lettuce at both 4 and 25°C (post-harvest)	(Yan et al., 2020)
Salmonella strains	T156; MOI 1000 and 10,000	Local wastewater (Wuhan)	Inhibition of *Salmonella* growth in artificially contaminated milk and lettuce (efficacy of 57.93% and 55.47%, respectively) at 4°C (post-harvest)	(Li et al., 2021a)
S. Enteritidis and *S.* Typhimurium	Pu20; MOI 1000 and 10,000	Sewage samples	Reduction of *Salmonella* cells in liquid eggs (egg white and yolk); higher effect at 4°C than 25°C, the maximum antibacterial efficiency was 91.30% and 92.40%, respectively (post-harvest)	(Zhang et al., 2021b)
Salmonella	S1; 4.9×10^9 PFU	Wastewater	Reduction of *Salmonella* cells in chicken model of infection, reduction level depends on time after treatment (pre-harvest)	(Gomez-Garcia et al., 2021)
Salmonella strains Including *S.* Enteritidis, *S.* Typhimurium, and *S. gallinarum*	Four-phage cocktail (8sent1748, 8sent65, 3sent1, and 5sent1); 3×10^7 PFU/g of feed or 2×10^6 PFU/bird/day	Bafasal™	Reduction of *Salmonella* (by more than 16 times, Δlog10 (CFU/g) = 1.21 log) content in caeca of birds infected with *S.* Enteritidis. Activity against *S.* Enteritidis, *S.* Typhimurium and *S. gallinarum* in spot tests (pre-harvest)	(Wójcik et al., 2020)
S. Typhimurium	Two phages (vB_SenM-2 and vB-Sen-TO17; 2×10^9 PFU/mL	Chicken feces	Elimination of *Salmonella* cells in chicken model of infection, the most efficient was treatment started 1 day after infection (pre-harvest)	(Kosznik-Kwasnicka et al., 2022)
S. Typhimurium	Two-phage cocktail (SPFM10 and SPFM14) (~4 log PFU/g)	Food processing plant (SPFM10) and pig feces (SPFM14)	Reduction of *Salmonella* colonization in different gut compartments. *Salmonella* counts were reduced by on average 1 log CFU/g in stomach tissue, colon, and cecum, and 2 log CFU/g in duodenum tissue of piglets (pre-harvest)	(Thanki et al., 2022)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in food	Reference
S. Enteritidis, *S.* Typhimurium, and *E. coli* O157:H7	PS5; 100 μL of 10 log PFU/mL)	Chicken products	Reduction of bacterial cells (≥1.2 log CFU/piece or mL) in row chicken skin, row beef, lettuce, whole fat pasteurized milk, and liquid egg. For example, in milk, phage PS5 reduced the viable counts of *E. coli* O157:H7 to under detection limit (<10 CFU/mL) (post-harvest)	(Duc et al., 2020)
E. coli ATCC 13706	Phages phT4A and ECA2 and two-phage cocktail (phT4A/ECA2); 5 PFU/mL (MOI 1) and 7 PFU/mL (MOI 100)	Sewage network of Aveiro, Portugal	Reduction of bacterial cells (~2.0 log CFU/g for artificially and ~0.7 log CFU/g for naturally contaminated cockles) (pre/post-harvest)	(Pereira et al., 2017)
Shiga-toxin-producing *Escherichia coli* (STEC)	Four-phage cocktail; 8 log PFU/mL	Commercial prototype	Reduction of *E. coli* STEC O157, O121, and O103 (0.4 to 0.7 log CFU/cm^2) on beef cattle hide pieces (post-harvest)	(Tolen et al., 2018)
Shiga-toxin-producing *E. coli* (STEC) O157:H7	PE37; 20 μL of 5×10^7 PFU/mL	Bovine intestine	Significant reductions in the viable cells of STEC in artificially contaminated beef stored at 25°C (2.3 log CFU/piece) and 8°C (0.9 log CFU/piece) (post-harvest)	(Son et al., 2018)
Enteropathogenic *E. coli* (EPEC) and Shiga-toxin-producing *E. coli* (STEC)	Six-phage cocktail; 8–9 log PFU/mL	Stool samples of patients with diarrhea	Reduction of both EPEC and STEC (reduction level depends on temperature) in meat and milk stored at 4, 24, and 37°C (post-harvest)	(Tomat et al., 2018)
Shiga-toxin-producing *E. coli* (STEC) O157:H7	vB_EcoM-ECP26; 6 log PFU/mL	Sewage sample from Seongnam Water Reclamation Center (Gyeonggi, South Korea)	Reduction of STEC on romaine lettuce to undetectable levels 5 days after phage exposure (pre-harvest)	(Park et al., 2020)
E. coli O157:H7	Phage cocktail; 5×10^6 and 1×10^7 PFU/g	EcoShield PX™	Significant reductions in *E. coli* O157:H7 levels (up to 97%) in beef chuck roast, ground beef, chicken breast, cooked chicken, salmon, cheese, cantaloupe, and romaine lettuce (post-harvest)	(Vikram et al., 2020b)
Shiga-toxin producing *Escherichia coli* (STEC)	Three-phage cocktail (FM10, DP16 and DP19); MOI 0.1, 1.0, and 10	Sewage, feces, bedding material of cattle	Reduction of *E. coli* cells on the cucumber surface stored at 25°C (1.97–2.01 log CFU/g) and 4°C (1.16–2.01 log CFU/g) for 24 h (post-harvest)	(Mangieri et al., 2020)

(Continues)

TABLE 1 (Continued)

Target bacteria	Phage and dosage	Phage source	Applications in food	Reference
E. coli O157:H7	Phages EP75 and EP335; 8 log PFU/mL	PhageGuard E™	Reduction of *E. coli* cells in Beef Rose Meat kept under vacuum and aerobic conditions; under both conditions phage cocktail reduced *E. coli* O157:H7 in beef by approximately 1.4 log (post-harvest)	(Shebs et al., 2019)
E. coli O157:H7	JN01; 100 μL or 200 μL of 9 log PFU/mL	Wastewater	Reduction of *E. coli* O157:H7 cells in UHT milk (2.96 CFU/mL in the control group after 3 days storage at 4°C, 1.5 log CFU/mL in phage-treated sample at the beginning of storage, and undetectable levels within 1–3 days of storage; raw beef (the numbers of *E. coli* O157: H7 in the phage-treated samples decreased to 2.5, 2.3, 1.7, 1.5, and 1.8 log CFU/cm^2 after stored at 4°C for 0, 1, 3, 5, and 7 days) (post-harvest)	(Li et al., 2021c)
E. coli O157:H7 *S.* Typhimurium	EscoHU1; 50 μL of 2×10^9 PFU/mL (milk) or 100 μL of 2×10^9 PFU/ cm^2 (beef)	River water in Hokkaido, Japan; *E. coli* O157:H7 RIMD 0509939 is the host strain	EscoHU1 suppressed the growth of *E. coli* O157:H7 in milk (1.2 log CFU/mL reduction at 72 h), and beef *E. coli* 1.7 log CFU/cm^2 reduction at 3 h in phage-treated samples; slight decrease (0.2 log CFU/cm^2) of *S.* Typhimurium in the beef stored for 72 h; the antimicrobial effect of phage on *S.* Typhimurium in milk was limited (post-harvest)	(Yamaki et al., 2022)
Shiga-toxin producing *E. coli* O26:H11	vB_EcoM_VR26 (VR26); 8 log PFU/cm^2	Isolated in Lithuania using *E. coli* MH1 strain as a host	Reduction of *E. coli* O26:H11 by approximately 2 log CFU/piece on lettuce at 4, 8, and 22°C (post-harvest)	(Zajančkauskaitė et al., 2021)
Pseudomonas lactis	Phage from raw cow's milk; 6×10^7 PFU	Raw cow's milk	Reduction (1000-fold compared to control) of viable bacterial cell in both skim and whole milk (post-harvest)	(Tanaka et al., 2018)
Shigella sonnei	Five-phage cocktail; 5–7 log PFU/g	ShigaShield™	Reduction of *Shigella* cells (>1 log units) in deli meat, smoked salmon, pre-cooked chicken, lettuce, and yogurt except for the lowest phage dose (9×10^5 PFU/g) on melon where reduction was only 0.25 log (post-harvest)	(Soffer et al., 2017)
Shigella flexneri	vB_SflS-ISF001; 8 log PFU/g	Wastewater	Reduction in the count of viable *S. flexneri* PTCC 1234 cells by ~2 logs in raw and cooked chicken breast 24 h after host inoculation; after 48 and 72 h, the numbers of viable *S. flexneri* cells were <100 CFU/g (post-harvest)	(Shahin & Bouzari, 2017)

The table is based on scientific reports from 2017 onward.

TABLE 2 Examples of commercially available bacteriophage products against Gram-negative foodborne pathogens.

Target	Name	Company	Reference
Campylobacter species including *C. jejuni* and *C. coli*	CampyShield™	Intralytix Inc.	(Vikram et al., 2022)
Salmonella spp.	Bafasal™	Proteon Pharmaceuticals	(Wójcik et al., 2020; Xu, 2021a)
	SalmoFresh™ (SalmoLyse®)	Intralytix Inc.	(Zhang et al., 2019); (Vikram et al., 2022)
	PhageGuard S™ (formerly Salmonelex™)	Micreos Food Safety	(Grant et al., 2017)
	SalmoPro®	Phagelux, Inc.	(Vikram et al., 2022)
	SalmoFREE®	Sciphage	(Clavijo et al., 2019)
E. coli O157:H7	EcoShield™ EcoShield PX™	Intralytix Inc.	(Vikram et al., 2022)
	Finalyse®	Passport Food Safety Solutions	(Polaska & Sokolowska, 2019)
	Ecolicide®> Ecolicide PX™	Intralytix Inc.	(Vikram et al., 2022)
	PhageGuard E™	Micreos Food Safety	(Shebs et al., 2020)
E. coli	Secure Shield E1	FINK TEC GmbH	(Vikram et al., 2022)
Salmonella spp., Shigella spp., Enteropathogenic serotypes of *E. coli*	EnkoPhagum	Brimrose Technology Corporation	(Polaska & Sokolowska, 2019)
Pseudomonas and *Aeromonas spp* in aquaculture	Bafador™	Proteon Pharmaceuticals	(Xu, 2021b)
Shigella	ShigaShield™	Intralytix Inc.	(Soffer et al., 2017)

The current trends in phage treatment against *Salmonella* spp. focus on the use of phages in various food matrices, that is, raw and ground poultry meat (Duc et al., 2018; Grant et al., 2017), milk (Huang et al., 2018; Islam et al., 2020b), juices, lettuce (Islam et al., 2019), eggs (Sonalika et al., 2020), iceberg lettuce and cucumber (Bai et al., 2019a), and the elimination of biofilms formed on surfaces in food processing plants (Islam et al., 2019; Islam et al., 2020a). The latest reports also indicate phage improvement strategies in terms of increasing their survival in the digestive tract of animals and under food processing conditions (Gomez-Garcia et al., 2021). In the context of specific food matrices, Huang et al. (2018) searched for highly effective phages against *S.* Typhimurium in milk, sausage, and lettuce. After screening, three phages with high anti-*Salmonella* potential were selected for further study. The phage LPST10 was the most effective and active over wide ranges of temperature (30–60°C) and pH (3–13), which indicated that LPST10 is a suitable candidate for use in the food processing environment. It was shown that the application of LPST10 significantly reduced the number of bacteria (in the range of 0.92–5.12 log CFU/sample) depending on the food matrix. Moreover, an increase in phage titer up to 2.96 log PFU/sample was observed in all tested food samples (Huang et al., 2018). In another study, Nale et al. (2021) evaluated 21 phages against *Salmonella* for biocontrol of this pathogen in poultry and swine. They showed that individual phages resulted in a reduction in the bacterial population within 6 h after phage application. However, the number of bacterial cells increased within the next hour. Therefore, a three-phage cocktail was composed and applied to a *Galleria mellonella* model infected with representative swine, chicken, and laboratory *Salmonella* strains. The phage cocktail was administered under three experimental conditions: 2 h before bacterial infection as a prophylactic tool, together with bacteria as a coadministration, and 2 h after bacterial infection. In all experimental variants, a reduction in the number of *Salmonella* cells was observed, and *G. mellonella* showed a higher survival rate. However, in the case of prophylactic use, the efficacy was the highest; notably, all larvae survived, and *Salmonella* cells were absent 72 h after phage application (Nale et al., 2021). In another study, Islam et al. (2019) showed a high efficiency of a phage cocktail of LPSTLL, LPST94, and LPST153 against *Salmonella* in milk and chicken breast samples. The final bacterial cell count was 3 log CFU/mL for milk and 3 log CFU/cm^2 for meat, and the samples were stored at either 25 or 4°C. After treatment with the phage cocktail (MOI of 1000 and 10000), *Salmonella* cells were reduced below the detection limit (<10 CFU per mL or cm^2), regardless of the storage temperature. Moreover, the phage cocktail was evaluated for eradication of *Salmonella* biofilm. Biofilms were formed in 96-well

microtiter plates and on stainless steel surfaces. It was shown that the application of the phage cocktail resulted in a reduction in the mass of the microplate biofilms in the range of 44%−63% and in the bacterial count on stainless steel surfaces in the range of 5.23–6.42 log units (Islam et al., 2019). Korzeniowski et al. (2022) also showed eradication of *Salmonella* biofilms formed in 96-well microtiter plates and on stainless steel surfaces with an effectiveness of up to 87% and 98%, respectively. Moreover, three-phage cocktail UPWr_S134 was shown to eliminate *S*. Enteritidis from a poultry drinker surface. In another study, Kosznik-Kwaśnicka et al. (2022) applied a cocktail of two phages (vB_SenM-2 and vB_Sen-TO17) to treat *S*. Typhimurium infection in chickens. When the treatment was applied 1 day following infection, *S*. Typhimurium was quickly eliminated from the chicken gastrointestinal tract, and the therapy was as effective as either enrofloxacin or colistin antibiotic therapy. Phage therapy appears to be less invasive than antibiotic therapy, as fewer changes in the chicken gastrointestinal microbiome are observed. In the report of Kosznik-Kwasnicka et al. (2022), phages were delivered orally as a suspension in 20 mM $CaCO_3$. The study by Thanki et al. (2022) emphasized the benefit of optimizing dried phage preparations administered to animals with feed. There, the authors showed that dried phages mixed with feed significantly reduced *Salmonella* colonization of the gastrointestinal tract of pigs.

3.3 | Shiga toxin-producing *Escherichia coli*

Another foodborne pathogen is STEC. The main cause of STEC infection is the consumption of contaminated, undercooked meat, unpasteurized milk, alfalfa sprouts, lettuce, and salami (Terajima et al., 2017). Symptoms usually appear 1−3 days after eating contaminated food and include bloody diarrhea, stomach cramps, and vomiting, whereas fever is rare (Hunt, 2010). With regard to treating STEC infection, the applicability of phage therapy has also been demonstrated. For instance, Tolen et al. (2018) evaluated the effect of a phage cocktail against STEC on beef cattle hide pieces. Pieces of beef cattle hide were artificially contaminated with STEC with a final cell count of ∼7 log CFU/mL, and then a commercial prototype of a phage cocktail was applied at MOIs ranging from 2.2 to 47.3. The use of this phage cocktail reduced *E. coli* O157, O121, and O103 counts to a level of 0.4–0.7 log CFU/cm^2, while the counts of *E. coli* O111 and O45 did not significantly decrease. Additionally, only the lowest doses of phage were needed for *E. coli* O157 and O121 cell lysis (Tolen et al., 2018). In another study, Tomat et al. (2018) evaluated the effect of a six-phage cocktail against enteropathogenic *E. coli* (EPEC) and STEC in milk, meat and Hershey-Mg broth stored at 4, 24, and 37°C. The phage cocktail was found to be more effective in food matrices stored at 24 and 37°C, achieving reduction levels of 2 to ≥4 and 3−4 log CFU/mL for milk and 2.6–4.0 and 3–3.8 log CFU/mL for meat at 24 and 37°C, respectively. In food matrices stored at 4°C for 48 h, the reduction level was 0.5–1.0 log CFU/mL (Tomat et al., 2018). These findings indicate the possibility of using a phage cocktail to control *E. coli* in milk and meat products, especially in sectors where refrigerated storage of the food products is not needed. In turn, Mangieri et al. (2020) evaluated phages isolated from different sources (sewage, feces, and bedding material of cattle) against STEC. They showed that some STEC isolates were sensitive to the phages used. Based on these results, three phages were selected and combined as a phage cocktail. The cocktail was used at different doses (MOI of 0.1, 1.0, 10) against STEC, with the highest MOI being the most effective dose. In the next step, the inhibitory effect of the cocktail against STEC on cucumbers stored under refrigerated conditions and at room temperature was evaluated. Under both storage conditions, the number of STEC decreased by 1−2 log units (Mangieri et al., 2020).

3.4 | *Yersinia enterocolitica*

Regarding *Yersinia enterocolitica* infections, there are an estimated 117,000 cases annually, 640 infected people required hospitalization, the mortality rate is 35 cases per year in the United States (Filik et al., 2022), and 5744 confirmed cases in 28 countries were reported in Europe (ECDC, 2022). The most common cause of yersiniosis is the consumption of raw or undercooked pork (Ukuku & Bari, 2022). Symptoms of *Yersinia* infection vary between children and adults. In children, they include abdominal pain, fever and diarrhea, usually bloody, while in adults, apart from fever, there is right-sided abdominal pain, often mistaken for appendicitis. Symptoms begin 4−7 days after exposure and may continue for more than 3 weeks (Ukuku & Bari, 2022). The effectiveness of phages has been evaluated against *Y. enterocolitica*. For instance, Jun et al. (2018) tested the phage fHe-Yen9-01, which has a broad host range, for control of *Y. enterocolitica* in raw pork, ready-to-eat pork, and milk. Phage application decreased the number of *Y. enterocolitica* cells by 1−2 log units in raw pork after 72 h of storage at 4°C, ready-to-eat pork after 12 h at 26°C, and milk after 72 h of storage at 4°C. Additionally, this phage effectively removed bacterial cells from kitchen utensils used to process food, for example, cutting boards and knives (Jun et al., 2018).

4 | COMMERCIALLY AVAILABLE PHAGE BIOPRESERVATION PRODUCTS

Phages are prospective antimicrobial alternatives for preventing contamination by bacterial pathogens at different stages of food production. Since the first approval of a phage cocktail as a food preservative by the US Food and Drug Administration (FDA) in 2006 (Vikram et al., 2020a), an increasing number of commercial phage products have become available for controlling foodborne pathogens.

Phage products approved by the US FDA for food safety applications inhibiting *Salmonella* growth are SalmoFresh™ (Intralytix, Inc.), PhageGuard S™ (formerly Salmonelex™) (Micreos Food Safety), and SalmoPro® (Phagelux) (Vikram et al., 2022) (Table 2). Zhang et al. (2019) compared the effectiveness of SalmoFresh™ (six-phage cocktail) with a chlorinated water treatment to reduce *Salmonella* on the surface of lettuce, mung bean sprouts, and seeds. The results showed that the combination of chlorination followed by administration of the phage cocktail was the most effective at reducing *Salmonella* on lettuce and sprouts. Seed treatment was not as effective because *Salmonella* was able to grow exponentially during germination (Zhang et al., 2019). PhageGuard S™ was tested recently to reduce *Salmonella* counts on skinless chicken meat (Grant et al., 2017), ground beef (Yeh et al., 2018), and skinless and skin-on poultry products (Hagens et al., 2018). In 2017, a patent was granted for another commercial product, SalmoFREE® (Sciphage), comprising six lytic phages for potential use as a *Salmonella* biocontrol agent in poultry products (Clavijo et al., 2019). Clavijo et al. (2019) used SalmoFREE® on a commercial broiler farm in Colombia. The results showed up to a 100% reduction in *Salmonella* incidence in the phage-treated group, while the pathogen was still detected in the control group. Moreover, the presence of SalmoFREE® in drinking water did not have any negative effect on production parameters such as weight, feed conversion, weight homogeneity, and mortality rate of chickens (Clavijo et al., 2019).

Fewer commercial products are directed against *E. coli* pathogenic serotypes such as O157:H7 and *Shigella* spp. EcoShield™ contains three lytic phages against *E. coli* O157:H7, Ecolicide® (Ecolicide PX™) and EcoShield PX™ (three to eight individual lytic phages) were developed by Intralytix, Inc. Other products, namely, Finalyse® and PhageGuard E™, also approved for food safety applications to eradicate *E. coli* O157:H7, were developed by Passport Food Safety Solutions and Micreos Food Safety, respectively (Vikram et al., 2022).

Recently, Vikram et al. (2020b) showed the efficacy of EcoShield PX™ against *E. coli* O157:H7 in eight food products: beef chuck roast, ground beef, chicken breast, cooked chicken, salmon, cheese, cantaloupe, and romaine lettuce. Application of EcoShield PX™ resulted in significant reductions in *E. coli* O157:H7 levels of up to 97% in all foods (Vikram et al., 2020b).

ShigaShield™ (Intralytix, Inc.) is also listed as Generally Recognized as Safe (GRAS) (Vikram et al., 2022). Soffer et al. (2017) showed the activity of ShigaShield™ in different foods, including melons, lettuce, yogurt, deli beef, smoked salmon, and chicken breast meat. The application of a *Shigella*-specific phage cocktail reduced the levels of *Shigella* by at least 1 log in all food types.

5 | PHAGE FORMULATIONS TO ENHANCE THE EFFECTIVENESS OF PHAGE ACTIVITY IN A FOOD MATRIX

Several approaches are used to protect phages from the undesirable effects of many food ingredients, such as organic acids, fatty acids, tannins, or the low pH of the gastrointestinal tract of animals (Xu 2021a). In the study of Gomez-Garcia et al. (2021), encapsulation (ionotropic gelation, alginate beads, calcium chloride, and bacteriophage S1 against *S. enterica*) was used as a novel approach to phage delivery in an in vivo chicken model. The aim of encapsulation was to protect the phage against the low pH of the stomach and to release it at a higher pH. The administration of encapsulated phage S1 to chickens infected with *Salmonella* resulted in the presence of phage in the duodenum and cecum 3 h after phage application, which emphasized the possibility of using encapsulated phages to eliminate *Salmonella* from the intestinal tract of chickens. In another study, encapsulation of *S.* Enteritidis phage f3αSE in alginate-Ca^{2+} spheres protected the phage against environmental conditions (Soto et al., 2018).

Chitosan and alginate are the two most studied natural polymers that have attracted interest as biocompatible vehicles for the delivery of antimicrobial agents (Niculescu & Grumezescu, 2022). The combination of these two agents has been recently investigated as a strategy to protect loaded bacteriophages from oxidation, enzymatic degradation, and hydrolysis. The addition of alginate increases the stability of chitosan, as the anionic nature of alginate complements the cationic backbone of chitosan. Moreover, alginate tends to shrink at low pH and dissolve at higher pH values, while chitosan dissolves at low pH and becomes insoluble at high pH values. Therefore, the creation of polyelectrolyte complexes between these two materials is beneficial in overcoming the limitations of each material. Studies on phage ZCEC5 encapsulation in chitosan-alginate beads have shown promising results in

targeting intestinal bacteria that cause zoonotic diseases such as *E. coli* O157:H7 in farm animals (Abdelsattar et al., 2019).

Eudragit® S100 and alginate microparticles have also been used to protect bacteriophages from the gastric acidic environment (Vinner et al., 2019). Vinner and Malik (2018) microencapsulated *Salmonella*-specific bacteriophage Felix O1 in a pH-responsive polymer formulation. Encapsulated phages previously exposed to simulated gastric fluid of pH 1.0 for 2 h were released at an elevated pH in simulated intestinal fluid and were able to arrest *Salmonella* growth. Moreover, Eudragit ES100/Alg (EK1F) microparticles have been shown to protect phages exposed to simulated gastric fluid at pH 2.0 for an exposure period of 2 h (Vinner et al., 2019).

A slightly different approach was presented in the study by Alves et al. (2020). They used phages and cinnamaldehyde in a sodium alginate emulsion, and the effect of this combination was evaluated against *E. coli* and *S.* Enteritidis. It was shown that the system containing phages EC4 and φ135 was effective against both pathogens, showing synergistic effects against *E. coli* and *Salmonella*, respectively. These findings indicate the possibility of applying this type of emulsion, for example, in the production of packaging, protecting food products against foodborne pathogens.

6 | FACTORS LIMITING THE USE OF PHAGES IN FOOD PRODUCTION

The cited studies prove the high application potential of phages and phage cocktails in ensuring the microbiological safety of food. Notably, the effectiveness of phages was assessed not only against pathogens but also by taking into account specific food matrices and biofilms, mimicking the real conditions of food processing plants. Nevertheless, the use of phages in the food industry has some limitations. First, phages are mostly highly specific, as they are active at the subspecies level or even the strain level (Abdelsattar et al., 2021). When several phages or phage cocktails are required to eliminate all strains of a certain species or a more challenging combination of different pathogenic species, the interactions between the different phages and their interactions with food components need to be investigated. Furthermore, the role of bacteriophages in the dissemination of antibiotic resistance genes via transduction cannot be overlooked. Wang et al. (2018) screened pig feces from three commercial farms in China for 32 clinically relevant antibiotic resistance genes and found *sul1*, bla_{TEM}, and *ermB* genes providing resistance to sulfonamides, β-lactams, and macrolides–lincosamide–streptogramin B, respectively, in all phage DNA samples. Subsequently, Yang et al. (2020) reported the presence of the colistin-resistant gene (*mcr-1*) in bacteriophage DNA isolated from chicken feces.

The elimination of biofilms in food processing plants is also challenging due to the physiological differentiation of cells within the biofilm structure and the presence of extracellular matrices with different chemical compositions (Gray et al., 2018). Moreover, phages comprise proteins that are sensitive to temperature, salinity, or acidity of the external environment, and these factors are variable or extreme in the food processing environment (Fister et al., 2016; Jończyk et al., 2011). For instance, Park et al. (2021) showed that exposure of *Salmonella* phages to a temperature of 70°C for 30 min affected phage stability. Additionally, there is a constant arms race between bacteria and coevelving with them bacteriophages (Ofir & Sorek, 2018). Bacterial defense systems tend to form "defense islands" in microbial genomes (Doron et al., 2018). As a result of mutations/deletions in the genes encoding phage receptors, CRISPR–Cas adaptive defense systems, retrons (systems consisting of three components, namely, a reverse transcriptase, a noncoding RNA, and an effector protein), the Zorya system (based on inhibition of phage DNA replication), BREX (bacteriophage exclusion), DISARM (defense island system associated with restriction–modification) and many others, bacteria acquire phage resistance (Doron et al., 2018; Millman et al., 2020; van Nieuwenhuyse et al., 2022). For example, retron Ec48 of *E. coli* guards the RecBCD complex with a central role in DNA repair and antiphage activity in bacteria. Inhibition of RecBCD by phage proteins activates the retron, leading to abortive infection and bacterial cell death, preventing lysis of the entire cell population (Doron et al., 2018). Interestingly, some bacteria displaying resistance to phages become more susceptible to antibiotics (Burmeister et al., 2020). For example, *E. coli* phage U136B, isolated from a pig farm in Connecticut in the United States, uses the antibiotic efflux pump protein TolC for infection. Since TolC contributes to *E. coli* antibiotic resistance, its spontaneous mutation causes resistance to phages but simultaneously reduces bacterial resistance to colistin, a polypeptide antibiotic in the polymyxin class (Burmeister et al., 2020). However, a different report showed increased resistance of *Pseudomonas aeruginosa* PAO1 against both 14/1 phage and antibiotic gentamicin due to biofilm growth, which provided a generalized resistance mechanism (Moulton-Brown & Friman, 2018).

Despite the available knowledge on the effectiveness of phages against bacterial cells organized into a biofilm, the analysis of their effectiveness against single-species biofilms on surfaces made of materials typical for surfaces in contact with food and the use of static conditions is a

major limiting factor. The available knowledge of phages against biofilms is mostly based on single-species biofilms, while in practice biofilms that typically form on materials used in food processing plants are dual or multi-species and grow, affecting the chemical composition of the extracellular matrix as well as quorum sensing, which in turn determines the biofilm's resistance to antibacterial preparations (Giaouris et al., 2015). In addition, a large part of the research is carried out on polystyrene surfaces in 96-well microtiter plates instead of, for example, on stainless steel or glass surfaces (Islam et al., 2019). A major disadvantage of research on biofilms is also their formation under laboratory conditions in a static system, which does not reflect the conditions of a food industry plant, where cell adhesion is hindered due to the flow of semifinished products as well as by washing and disinfection procedures. Under these conditions they form biofilms with greater resistance than their planktonic counterparts (Kocot et al., 2021), and further research is needed on the application of phages against biofilms, taking into account the conditions that better mimic the conditions of food production plants. Alternatively, a newer avenue of investigation is the use of phage lysins, which are less prone to promoting the development of resistance and often active against biofilms (Fischetti, 2018).

7 | PHAGE-DERIVED LYSINS

A bacteriophage interferes with a bacterium at multiple stages during its replication cycle. Different phage proteins may therefore have antibacterial potential, with phage lysins by far being investigated most intensively (Oliveira et al., 2018). Phage lysins are lytic enzymes that degrade PG. They are used at the initiation of infection and during the lysis phase at the end of the phage replication cycle. For infection, phages harbor a virion-associated lysin that creates a local, small hole for phage genome ejection from the capsid (Grabowski et al., 2021). During lysis, a vast amount of a different phage lysin (termed endolysin) accumulates in the cytoplasm and is suddenly released to the periplasm, resulting in abrupt and massive PG degradation, osmotic lysis, and dissemination of the newly produced progeny (Oliveira et al., 2018). Phage lysins can be produced in a recombinant way and added exogenously to bacteria to kill them by instantaneous PG hydrolysis (Nelson et al., 2001). The specificity of lysins is generally broader than that of phages and is usually at the genus or species level. These hydrolytic enzymes are able to destroy the cell walls of Gram-positive bacteria, but their use in the context of Gram-negative bacteria is limited (Murray et al., 2021). This limitation is dictated by the differences in cell wall structure. The factor limiting the effectiveness of the lysin against Gram-negative bacteria is the presence of the OM that surrounds the PG layer and thus hinders its degradation by phage lysins (Schmelcher & Loessner, 2016). The OM is composed of phospholipids, lipopolysaccharides, and OM proteins. The lipopolysaccharide layer is firmly interconnected through divalent cations that bridge the phosphate groups of adjacent lipopolysaccharide molecules by ionic interactions (Murray et al., 2021).

Generally, endolysins targeting Gram-negative bacteria have a globular structure with a single domain having catalytic activity. In contrast, endolysins active on the Gram-positive cell wall have a modular architecture (Briers et al., 2009). Basically, the structure of such modular endolysins depends on the presence of at least one enzymatically active domain (EAD) and a cell wall-binding domain (CBD), which are connected with a short linker region (Schmelcher et al., 2012). The EAD is mostly found at the N-terminal end and is the proper catalytic part of the enzyme. In turn, the CBD is located at the C-terminal end or has a central position and is responsible for the specific recognition of ligands present in the bacterial cell wall. Virion-associated lysins comprise a single EAD connected to structural domains that link the EAD needed for infection to the virion structure. An EAD may be named by its specific cleavage site in the PG. According to this classification, endolysins can be classified as endopeptidases, muramidases, amidases, glucosaminidases, and transglycosylases (Abdelrahman et al., 2021). In turn, the CBD determines the specificity of the endolysin, which is defined by the specific ligand that is targeted. The specificity of endolysins, similar to bacteriophages, allows their use as a narrow spectrum antibacterial, which is considered microbiome friendly. Nevertheless, the specificity of phage lysins is mostly at the species or genus level, whereas phages are generally specific at the subspecies level. The use of lysins in the food industry faces similar obstacles as the application of phages, but the important differentiator of phage-derived lysins is the lower probability of resistance development, while phages are unique in their autodosing and evolution capacity.

The efficiency of endolysins against Gram-positive bacteria has been reported many times (Chang, 2020; Ibarra-Sánchez et al., 2018; Misiou et al., 2018; Nelson et al., 2001; Oliveira et al., 2012). Notably, the activity of lysins against Gram-positive bacteria was demonstrated in food matrices and in specific food products, which clearly indicates the possibility of their application in combating foodborne pathogens in the food sector. Nevertheless, the widespread use of lysins in the food industry is limited mainly due to the need for their large-scale production, purification process, and scalability, which may entail high costs (Xu, 2021a). A new approach to reducing these limitations is

the use of nonbacterial expression systems such as algae, plants, and animals, which is currently under investigation (Kovalskaya et al., 2016; Starkevič et al., 2015; Stoffels et al., 2017). In addition, previous research on lysins has mostly focused on their medical use and they are under clinical evaluation, for example, lysins CF-301, P128, SAL200, and XZ.700 (Kuiper et al., 2021; https://www.trialregister.nl/trial/8876). However, in recent years, research on the antibacterial potential of lysins in the food sector has been increasingly undertaken (Liu et al., 2019; Xu et al., 2021b), driven by the need for innovative antibacterials targeting Gram-negative foodborne pathogens. The studies till date on the use of lysins against Gram-negative bacteria are reported in Table 3.

Some reports have evaluated the effectiveness of lysins in combating Gram-negative bacteria in the food matrix of lettuce, specifically for the elimination of *Salmonella* (Liu et al., 2019) and *E. coli* O157:H7 (Xu et al., 2021b). In the first study, Liu et al. (2019) characterized LysWL59 from phage LPST10. They showed that the enzyme is active in the range of pH 6–10 and at a temperature of 4–90°C, indicating the application potential under diverse conditions of technological processes in the food industry. Moreover, the application of the enzyme at a concentration of 2.5 μM supported by 0.5 mM EDTA resulted in a reduction of 93.03% of *S*. Typhimurium on the lettuce within 1 h (Liu et al., 2019). In the second study, Xu et al. 2021b evaluated the activity of a new PlyEc2 enzyme, identified as *E. coli* lysin, against key foodborne pathogens. They showed that the enzyme PlyEc2 at a concentration of 100 μg/mL was active against the *E. coli* O157:H7 strain *sakai* (ATCC BAA460) at various pH values (range 6–9), killing more than 5 log units of bacteria at pH 7.0, pH 7.5, and pH 8.5. Moreover, the enzyme eliminated 99.7% of *E. coli* O157:H7 (reduction of 2.59 ± 0.12 log units) on romaine lettuce leaves and showed killing activity against *Salmonella, Acinetobacter, Pseudomonas* (>5 log units), and *Shigella* (~4–5 log units). In addition, the enzyme killed 99.8% of the microbes (reduction of 2.93 ± 0.14 log units) present in the washing solutions, indicating an additional benefit in terms of use in the food industry, preventing food cross-contamination during washing (Xu et al., 2021b). The activity of lysin PlyEc2 against Gram-negative bacteria is probably due to the presence of a highly positively charged C-terminal region (40 amino acids) that may be responsible for outer membrane permeabilization (Xu et al., 2021b).

Other studies on the usefulness of lysins in the food industry focus on assessing their effectiveness in external conditions that mimic different stages or conditions of the production process, such as temperature, pH, ionic strength (Ding et al., 2020; Legotsky et al., 2014), and the presence of slightly acidic hypochlorous water (Zhang et al., 2021a), which can mimic a disinfection treatment. Nevertheless, the number of scientific reports on the use of lysins in other specific food matrices is limited. As mentioned, the major limiting factor is the presence of an OM that hinders the interaction of the enzyme with the PG layer. Therefore, the scientific community is developing and evaluating variable solutions to increase the potential of lysins to eliminate Gram-negative bacteria.

8 | STRATEGIES TO IMPROVE THE ACTIVITY OF LYSINS AGAINST GRAM-NEGATIVE BACTERIA

Lysins can be divided into three generations. According to this classification, the first generation includes wild-type (native) lysins with antimicrobial properties; the second generation is represented by engineered lysins with improved antimicrobial and biochemical properties, higher stability, and activity against Gram-negative bacteria; and the third generation is associated with improved pharmacodynamic and pharmacokinetic properties (de Maesschalck et al., 2020). Due to their modular structure, lysins are a rewarding object to be modified with the use of advanced tools of molecular engineering to obtain enzymes with the desired properties (Dong et al., 2015; Kashani et al., 2017). In this section, we present current strategies for the improvement of lysins to combat Gram-negative bacteria (Figure 1).

8.1 | Lysins and OM permeabilizers

The simplest strategy to overcome the OM barrier is the use of OM permeabilizers. In this context, the most commonly used permeabilizer is EDTA, which functions by chelating the stabilizing divalent cations from the OM. For instance, Walmagh et al. (2012) evaluated the antibacterial activity of three different endolysins against Gram-negative bacteria—OBPgp279, PVP-SE1gp146 and 201φ2-1gp229—in the presence of EDTA. Although OBPgp279 had intrinsic antibacterial activity against selected Gram-negative pathogens, the addition of 0.5 mM EDTA decreased the counts of bacterial cells by another 2–3 log units. In another study, Oliveira et al. (2014) conducted a comprehensive study on the effectiveness of endolysin Lys68. This enzyme is only inactivated after exposure to a temperature of 100°C for 30 min and retained 76.7% of its activity when stored at 4°C for 2 months, supporting its use under the diverse conditions prevalent in the food industry. The supplementation of this endolysin with compounds such as EDTA, citric and malic acids resulted in the extension of the enzyme's spectrum of activity, showing efficiency against 13 species of Gram-negative bacteria. In the

TABLE 3 Phage lysins tested against foodborne Gram-negative pathogens.

Target bacteria	Phage lysin	Lysin source	Observations	Reference
Several Gram-negative pathogens, particularly *Salmonella* Typhimurium	Lys68	*Salmonella* phage phi68 isolated from feces from a poultry farm	Higher anti-biofilm effect under treatment supported with malic or citric acid. Maximal reduction of 5 logs in *S*. Typhimurium load/CFU after 2 h treatment with Lys68/citric acid; potential control of Gram-negative pathogens in the food industry	(Oliveira et al., 2014)
S. Typhimurium	LysWL59	Bacteriophage LPST10	Reduction of *S*. Typhimurium on lettuce especially in the presence of 0.5 mM EDTA (post-harvest)	(Liu et al., 2019)
S. Enteritidis, *S*. Typhimurium, *Salmonella* Argora, Indiana, Anatum, and Dublin, *E. coli*	LysSE24	*Salmonella* phage LPSE1	Activity against all tested Gram-negative bacterial strains in the presence of OMPs; potential role in food industry	(Ding et al., 2020)
S. Typhimurium	LysSTG2	*Salmonella* phage STG2	Reduction of the viability of *S*. Typhimurium planktonic cells by 1.2 log. Activity against 72 h S. Typhimurium biofilm formed in the microplate, especially after sequential treatment with slightly acidic hypochlorous water and LysSTG2; potential role in food industry	(Zhang et al., 2021a)
S. Enteritidis, *S*. Typhimurium	EN4	*Salmonella* phage TYM102	Reduction of 1.0–1.6 log CFU/g of *Salmonella* cells in chilled and thawed raw chicken meat in the presence of 0.1% $NaHCO_3$ (post-harvest)	(Abhisingha et al., 2023)
E. coli CR63	Lys394	*Salmonella* phage S-394	Reduction of 4 logs of *E. coli* cells after 30 min treatment in the presence of 50 μg/mL of antimicrobial peptide PGLa and 1 mM EDTA	(Legotsky et al., 2014)
E. coli	Lysep3	*E. coli* phage vB_EcoM-ep3	Reduction of *E. coli* DH5a within 2 h in the presence of 25 mM EDTA in in vitro antibacterial tests. Host phage lysed 9 out of 15 multidrug-resistant *E. coli* strains isolated from chickens (pre-harvest)	(Lv et al., 2015)
E. coli O157:H7	PlyEc2	*E. coli* phage	Active against key Gram-negative pathogens including *E. coli*, *Salmonella*, *Shigella*, *Acinetobacter*, and *Pseudomonas* in killing assays. Reduction of *E. coli* O157:H7 on contaminated lettuce (post-harvest)	(Xu et al., 2021b)
E. coli O157:H7	rLysJN01	*E. coli* phage JN01	Reduction of viable *E. coli* cells on lettuce by 78.4% and 97.8% with the treatment of 30 μg/mL and 60 μg/mL of rLysJN01 for 60 min, respectively, at 25°C in the presence of 0.5 mM EDTA (post-harvest)	(Shen et al., 2022)
Twenty-three Gram-negative bacterial strains including 10 strains of *Salmonella enterica* and 6 strains of *E. coli*	SPN9CC	*Salmonella* phage SPN9CC	Exogenous lytic activity against *E. coli*; SPN9CC endolysin reduced the number of viable *E. coli* cells by approximately 2 logs within 2 h; all Gram-negative bacterial strains after treatment with 100 mM EDTA were lysed in vitro by SPN9CC endolysin; potential role in food industry	(Lim et al., 2014)
Vibrio parahaemolyticus	Lysqdvp001	*Vibrio* phage qdvp001	The most stable cationic guar gum liposome formulation L-C_2 killed 99 % of *V. parahaemolyticus* in the seawater with live clams (pre-harvest)	(Ning et al., 2023)

The table is based on scientific reports from the last 10 years.

Abbreviations: EDTA, ethylenediaminetetraacetic acid; OMP, outer membrane permeabilizer.

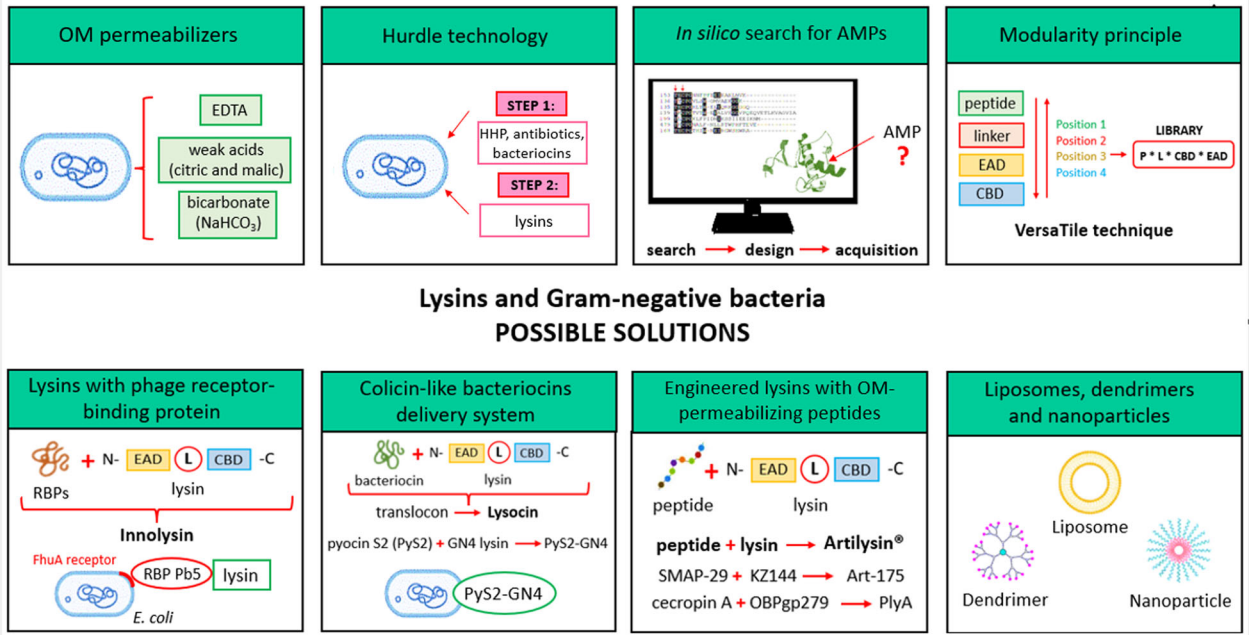

FIGURE 1 Selected methods of increasing the effectiveness of lysins against Gram-negative bacteria. AMPs, antimicrobial peptides; CBD, cell binding domain; EAD, enzymatic active domain; EDTA, ethylenediaminetetraacetic acid; HHP, high hydrostatic pressure; L, linker; OM, outer membrane; P, peptide; RBPs, receptor binding proteins; RBP Pb5, phage receptor-binding protein Pb5, irreversible binding to the FhuA receptor.

presence of 0.5 mM EDTA, Lys68 showed efficacy only against *Pseudomonas* strains. However, the presence of 2 mM citric and 5 mM malic acids broadened the effectiveness of Lys68 against other Gram-negative pathogens, including *S*. Typhimurium LT2. It was shown that in the presence of weak acids, Lys68 decreased the number of *Salmonella* cells by approximately 3–5 log units in solution in contrast to negative controls with the weak acids only. In addition, the number of cells in a biofilm decreased by approximately 1 log unit. Lys68 shows a relatively higher muralytic activity at lower pH values, and the use of acids contributed to a local decrease in the pH, explaining the advantage of using acids over EDTA as OM permeabilizer (Oliveira et al., 2014).

8.2 | Hurdle technology

One possibility to increase the effectiveness of endolysins against Gram-negative bacteria is the use of hurdle technology (Mukhopadhyay & Gorris, 2014). This approach involves the use of more than one method to eliminate pathogens and to ensure the microbiological safety of food. With regard to lysins, the method assumes the use of another treatment beforehand, which aims to breach the cell membranes, including the OM, subsequently allowing the lysin to interact with the target PG (Oliveira et al., 2012). One of the most commonly used processes, where the synergistic and subsequent effect of lysins is used, is the use of high hydrostatic pressure (HHP) technology. For instance, Briers et al. (2008) evaluated the synergy of HHP and two phage-encoded endolysins, KZ144 and EL188, in the control of *P. aeruginosa* PAO1. They showed that when the endolysins were added, lower pressures are needed to achieve the same killing, making this approach more affordable, particularly for food that cannot be pasteurized (e.g., guacamole, oysters) (Briers et al., 2008). Other strategies include demonstrating a synergistic effect between antibiotics (Letrado et al., 2018) or bacteriocins (García et al., 2010b) and endolysins, but studies dedicated to Gram-positive bacteria dominate here. Thus, this area is still open to research on Gram-negative bacteria.

8.3 | Lysins engineered with outer membrane-permeabilizing peptides

Lysins that degrade the PG of Gram-negative bacteria have been engineered with peptides that have the ability to destabilize or penetrate the OM. This self-promoted uptake mechanism of peptides promotes the uptake of the lysin moiety throughout the OM into the periplasm, where the lysin can degrade the PG layer (Briers et al., 2014a). Such engineered lysins are developed as Artilysin®s (Lysando). A series of experiments to design Artilysins and to evaluate their effectiveness against Gram-negative bacteria were

performed. A lead example is Artilysin Art-175, which consists of the KZ144 endolysin and the sheep myeloid antimicrobial peptide (SMAP-29) (Briers et al., 2014b). This engineered lysin is able to penetrate the OM and kill a diversity of *P. aeruginosa* strains, including multidrug-resistant (MDR) strains with up to a 5-log reduction in cell number. Furthermore, serial exposure to subinhibitory doses of Art-175 did not elicit resistance development, and no cross-resistance with resistance mechanisms of 21 therapeutic antibiotics was observed. A high bactericidal effect has also been reported against *Acinetobacter baumannii* (reduction of ≥8 log units) and its persisters (reduction of 2.35 ± 0.42 log units in the absence of 0.5 mM EDTA) (Defraine et al., 2016) and colistin-resistant *E. coli* isolates from swine, cattle, and chicken (reduction of 4.4 to 5.1 log units) (Schirmeier et al., 2018). In another study, Yang et al. (2015) designed a new engineered lysin, PlyA, by fusing the lysin OBPgp279 with a fragment of the cecropin A peptide (residues 1–8 KWKLFKKI). The activity of this modular enzyme was assessed against *A. baumannii* and *P. aeruginosa*. It was shown that PlyA was effective against both tested species in the exponential growth phase, while the activity decreased against cells in the stationary growth phase. The effectiveness of PlyA against cells in the stationary growth phase was enhanced by the use of OM permeabilizing compounds such as EDTA and citric acid. However, a further study showed that this particular engineered lysin was ineffective in culture medium, milk matrix, and serum. In turn, Ma et al. (2016) created constructs composed of the Lysep3 lysine (targeting *E. coli*) and a polypeptide containing either 5, 10, or 15 cationic amino acids or a polypeptide containing both cationic and hydrophobic amino acids. The construct with a polypeptide of 15 cationic amino acids was the most effective against *E. coli* (antibacterial reduction was 9%–42%) and showed killing effects against three other Gram-negative bacteria: *P. aeruginosa* (38 ± 3% reduction), *Salmonella* spp. (17 ± 2% reduction), and *Shigella* spp. (8 ± 2% reduction). Interestingly, the effectiveness of constructs containing cationic amino acids increased with the length of the chain.

8.4 | Innolysins

The concept of *innolysins* focuses on the binding of endolysins with phage receptor-binding proteins (RBPs) (Zampara et al., 2018). The first reported study (Zampara et al., 2020) described a chimera composed of endolysin and the phage RBP Pb5, both from phage T5. This protein binds irreversibly to the FhuA receptor. By using various combinations with or without flexible linkers, 12 constructs were obtained. The innolysins were tested against *E. coli*, and muralytic activity was observed. The reduction in *E. coli* cell counts suggests that these innolysins overcome the OM barrier and degrade the PG. Furthermore, an *E. coli fhu*A deletion mutant was used to demonstrate that the FhuA receptor is needed for the antibacterial activity of the selected innolysin Ec6. In addition, the selected innolysin was found to be active against other bacterial species carrying FhuA homologs, such as *Shigella sonnei* and *P. aeruginosa*. In a follow-up study by Zampara et al. (2021), they expanded the innolysin concept to the foodborne pathogen *C. jejuni*. A novel *C. jejuni*-specific RBP, the H-fiber originating from a prophage region of *C. jejuni* CAMSA2147, was identified. This H-fiber was fused to different enzymatic activity domains of endolysins. The in vitro study revealed innolysins Cj1 and Cj5 as the best fusion proteins to eliminate *C. jejuni* from contaminated chicken skin stored at 5°C. Both Cjs showed a reduction level over 1 log unit under these settings. Moreover, the authors point to the need to search for more new phage RBPs to improve the efficiency of innolysins against *C. jejuni*. While only shown for *E. coli* and *C. jejuni*, the innolysin concept could be more widely explored for other pathogens.

8.5 | Lysocins

The concept of *lysocins* relies on the use of delivery systems from colicin-like bacteriocins for translocation across the OM (Heselpoth et al., 2019). Colicin-like bacteriocins form translocons that transport catalytic (bactericidal) domains through protein channels in the OM. Lukacik et al. (2012) and Yan et al. (2017) used bacteriocin-lysin hybrid molecules derived from pesticin (targeting the FyuA OM protein) and colicin A (targeting vitamin B12 transporter, BtuB), respectively, to actively transport lysins across the OM of Gram-negative bacteria. In 2019, Heselpoth et al. evaluated a lysin-bacteriocin fusion protein (PyS2-GN4) containing the translocation domains of pyocin S2 (PyS2) and GN4 lysin. In this molecule, the PyS2 domains are responsible for translocation through the OM, whereas the GN4 lysin degrades the PG. A series of experiments showed 2 to 4 log reductions in planktonic *P. aeruginosa* cells at PyS2-GN4 concentrations between 0.1 and 100 μg/mL, in addition to activity against biofilms, activity in serum, and antipseudomonal efficacy in a murine model of bacteremia. Mice treated with 25 mg/kg of lysocin were 100% protected from death, and organs of lysocin-treated mice did not show any detectable *Pseudomonas* bacteria. These results are promising and seem to be a potential tool for the effective elimination of pathogens not only in the clinical context but also with regard to food pathogens. However, similar to innolysins, the protein dependence of lysocins

for uptake is expected to render the approach more susceptible to resistance development due to mutations or deletions, which could, however, also be associated with virulence loss.

8.6 | Modularity principle

All the approaches above are characterized by modularity, meaning that the fusion proteins are composed of modules from different origins. Shuffling these modules results in modular proteins with diverse biochemical and antibacterial properties (Schmelcher et al., 2012). This modularity principle can be boosted by the use of the VersaTile technique, which is a combinatorial DNA assembly method dedicated to constructing large and complex libraries of modular proteins. This technique has been applied to lysins engineered with OM-permeabilizing peptides (Artilysin concept; Briers et al., 2014a) and innolysins (Zampara et al., 2020). VersaTile allows shuffling of nonrelated DNA sequences without the need for traditional restriction/ligation. Instead, type IIS restriction enzymes are used to cut outside their recognition site with the possibility to freely choose the restriction site. A library of approximately 10,000 variants was created in a single day using this technique (Gerstmans et al., 2020). The leading variant 1D10 completely killed two *A. baumannii* strains (NCTC 13423 and RUH 134) in 50% human serum and slowed biofilm formation in an *ex vivo* pig skin model of burn wound infection (Gerstmans et al., 2020). The same technique was used to create the innolysins described above (Zampara et al., 2020), where the leading variant Ec21 was effective against *E. coli* resistant to third-generation cephalosporins isolated from production animals and meat. Three out of six selected *E. coli* strains were sensitive to the innolysin Ec21, with a reduction reaching 3.31 ± 0.53 log units. The VersaTile technique is promising, and although it has been mainly tested to identify engineered lysins useful in therapeutic applications, the method is generic and can also be targeted to food pathogens.

8.7 | *In silico* search for antimicrobial peptides

Some lysins comprise peptides, usually in their C-terminus, that exert a strong antibacterial effect that is not based on PG degradation (Szadkowska et al., 2022). Such antimicrobial peptides (AMPs) are responsible for the natural ability of some lysins to permeate the OM of Gram-negative bacteria. Vázquez et al. (2021) performed a bioinformatic analysis of the C-terminal ends of lysins directed against *Pseudomonas*. The assessment of the physicochemical properties allowed for the estimation of the probability of AMP occurrence based on the k-nearest neighbors (kNN) predictive model. The authors selected lysin variants with such peptides that may interact with the OM, and they showed that two variants, Pae87 and Ppl65, had muralytic and bactericidal activity against *P. aeruginosa* and other Gram-negative bacteria. Thus, the concept of predicting AMP-like regions seems to be a good strategy for the search for, design of and, consequently, the acquisition of phage lysins with an intrinsic antibacterial activity that can constitute the basis for further engineering.

8.8 | Lysin-based dendrimers

Another concept to improve the antimicrobial properties of phage lysins is the use of dendrimers. Dendrimers are organic chemical compounds with a regular, branched structure composed of sequentially linked multifunctional units (Markowicz-Piasecka & Mikiciuk-Olasik, 2016). Due to their structure and properties, dendrimers are an excellent vehicle for drugs and genes (Sheveleva et al., 2019). Until now, dendrimers have been mainly used in studies as vehicles for therapeutic substances that are already used in clinical practice (Gorzkiewicz et al., 2020; Popova et al., 2017). However, in a recent study by Quintana-Sanchez et al. (2022), the antimicrobial activity of a cationic carbosilane dendrimer was evaluated in combination with endolysin KP27, and the antibacterial activity of the mixture against *P. aeruginosa* PAOI was higher than that of the enzyme alone (Quintana-Sanchez et al., 2022). Notably, the structure of dendrimers also enables lysins to be protected against the influence of external factors related to technological processes (e.g., high temperatures, pH changes) and to maintain the antibacterial activity of lysins in the final food product. In summary, the dendrimer-lysin concept should be further explored to assess its potential to target a broad panel of bacteria, including foodborne pathogens.

8.9 | Liposome-mediated lysin delivery

Liposomal encapsulation of lysins has been reported to increase the effectiveness of endolysins against Gram-negative bacteria (Bai et al., 2019b). This approach has been demonstrated for the phage-derived lysin BSP16Lys using cationic liposomes composed of dipalmitoylphosphatidylcholine (DPPC), cholesterol, and hexadecylamine. The activity of this encapsulated enzyme was evaluated against *S.* Typhimurium and *E. coli*, and reduction levels of approximately 2 log CFU/mL were obtained for both strains. In one study (Ning et al., 2023), lysin-loaded liposome

systems containing octadecylamine, cationic guar gum (CGG), or liposomes coated with CGG were used to eliminate *Vibrio parahaemolyticus*, the major agent responsible for seafood-borne bacterial illnesses. The most stable CGG liposome formulation, L-$C_{2,}$ decreased the number of *V. parahaemolyticus* cells in infected clams from 6.62 to 4.85 and 4.54 log CFU/g at a final Lys lysin concentration of 25 and 50 μg/mL, respectively. That studies support the usefulness of liposome embedded lysin for controlling *V. parahaemolyticus* contamination in food and aquaculture fields.

The solution of encapsulating phage-derived lytic proteins in the structure of liposomes seems to be a prospective tool for combating Gram-negative bacteria, especially since the high efficiency does not require additional support with OM permeabilizers and can be combined with the abovementioned engineering methods. Liposomes, similar to dendrimers, can also have a protective function, which can maintain the activity of lysins during food processing, influencing the microbiological quality of food.

8.10 | Encapsulation in alginate-chitosan nanoparticles

One of the strategies to increase the effectiveness, especially therapeutic effectiveness, of lysins is encapsulation in alginate-chitosan nanoparticles (Alg-Chi NPs) (Gondil & Chhibber, 2021). Chitosan-based formulations have an advantage over other delivery systems because they increase the bioavailability of the therapeutic agent and are also safely removed from the host after release of the agent (Gondil & Chhibber, 2021). For instance, Kaur et al. (2020) used this strategy to increase the clinical utility of LysMR-5 with high lytic activity against MRSA and *Staphylococcus epidermidis* but with low stability and short half-life in vivo. It was shown that formulating LysMR-5 in the Alg-Chi NP complex increased the bactericidal properties against *S. aureus*. In addition, a biphasic release profile was observed under physiological pH conditions (pH 7.2). Moreover, the hemocompatibility and cytotoxicity assays confirmed the applicability of this delivery system for in vivo studies. The results of these studies indicate the promising potential of Alg-Chi NPs as a drug delivery system for in vivo research (Kaur et al., 2020). Nevertheless, scientific reports on the use of Alg-Chi NPs as a delivery system for lysins targeting Gram-negative bacteria are lacking.

In summarizing the methods of improving lysins in terms of their effective application against Gram-negative bacteria, it should be noted that engineered lysins are mainly tested as an application against human pathogenic strains intended for use in the clinic. It is worth remembering that food contamination and food poisoning remain global problems. Therefore, the methods used to improve lysins in the fight against Gram-negative bacteria should also be carried out against Gram-negative foodborne pathogens, taking into account specific food matrices, which may contribute to the creation of an effective strategy for the elimination of these pathogens and the prevention of foodborne diseases.

9 | CONCLUSIONS AND FUTURE PERSPECTIVES

Annual reports by the WHO indicate that foodborne diseases are a real global problem even in the 21st century when the awareness and advancement of cleaning and disinfection methods are at an unprecedentedly high level. Therefore, it is necessary to search for new and more effective methods of combating pathogens in the food processing environment. Additionally, the problem of antibiotic resistance makes the search for alternative antimicrobials an overriding goal of the scientific community. Most bacteria prevalent in the food industry and the clinic are Gram-negative bacteria. Therefore, the development of new antibacterials should target this group of bacteria.

In recent years, phages and phage lysins have been extensively tested for use as antibacterials. Phages have already been studied fairly well in the food context. The high effectiveness against foodborne pathogens in food matrices, in biofilms, and under food storage conditions has been extensively documented and has resulted in the development of commercially available phage preparations approved for use in food (Table 2). In turn, the use of phage lysins in a food context is largely limited to Gram-positive bacteria, with only a few studies focusing on the use of phage lysins against foodborne Gram-negative pathogens in food matrices. In recent years, different strategies to improve the effectiveness of phage lysins against Gram-negative bacteria have been reported. Nevertheless, it should be noted that most of this research is focused on clinical application. Therefore, future research should focus on the control of persistent foodborne pathogens, taking into account various food products, biofilms, and storage conditions.

Overall, phage-derived lysins represent a promising tool for combating Gram-negative pathogens in both the food processing and healthcare sectors. The use of advanced molecular biology tools will help in generating constructs with high activity against Gram-negative bacteria, which, in the near future, may promote the development of "next-generation lysins" that can be applied in the food sector.

AUTHOR CONTRIBUTIONS

Aleksandra Maria Kocot: Conceptualization; Data curation; Formal analysis; Visualization; Writing—original draft; Methodology; Writing—review & editing; Investigation. **Yves Briers**: Supervision; Writing—review & editing. **Magdalena Plotka**: Conceptualization; Writing—review & editing; Supervision; Funding acquisition; Writing—original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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REFERENCES

Abdelrahman, F., Easwaran, M., Daramola, O. I., Ragab, S., Lynch, S., Oduselu, T. J., Khan, F. M., Ayobami, A., Adnan, F., Torrents, E., Sanmukh, S., & El-Shibiny, A. (2021). Phage-encoded endolysins. *Antibiotics*, *10*(2), 124. https://doi.org/10.3390/ANTIBIOTICS10020124

Abdelsattar, A. S., Abdelrahman, F., Dawoud, A., Connerton, I. F., & El-Shibiny, A. (2019). Encapsulation of *E. coli* phage ZCEC5 in chitosan-alginate beads as a delivery system in phage therapy. *AMB Express*, *9*(1), 87. https://doi.org/10.1186/S13568-019-0810-9

Abdelsattar, A. S., Safwat, A., Nofal, R., Elsayed, A., Makky, S., & El-Shibiny, A. (2021). Isolation and characterization of bacteriophage ZCSE6 against *Salmonella* spp.: Phage application in milk. *Biologics*, *1*(2), 164–176. https://doi.org/10.3390/biologics1020010

Abhisingha, M., Dumnil, J., & Pitaksutheepong, C. (2023). Effect of lysin EN4 in combination with sodium bicarbonate on reduction of *Salmonella* in chilled and thawed chicken meat. *International Journal of Food Microbiology*, *387*, 110058. https://doi.org/10.1016/J.IJFOODMICRO.2022.110058

Alves, D., Cerqueira, M. A., Pastrana, L. M., & Sillankorva, S. (2020). Entrapment of a phage cocktail and cinnamaldehyde on sodium alginate emulsion-based films to fight food contamination by *Escherichia coli* and *Salmonella Enteritidis*. *Food Research International*, *128*, 108791. https://doi.org/10.1016/J.FOODRES.2019.108791

Bai, J., Jeon, B., & Ryu, S. (2019a). Effective inhibition of *Salmonella* Typhimurium in fresh produce by a phage cocktail targeting multiple host receptors. *Food Microbiology*, *77*, 52–60. https://doi.org/10.1016/J.FM.2018.08.011

Bai, J., Yang, E., Chang, P.-S., & Ryu, S. (2019b). Preparation and characterization of endolysin-containing liposomes and evaluation of their antimicrobial activities against Gram-negative bacteria. *Enzyme and Microbial Technology*, *128*, 40–48. https://doi.org/10.1016/J.ENZMICTEC.2019.05.006

Bintsis, T. (2017). Foodborne pathogens. *AIMS Microbiology*, *3*(3), 529. https://doi.org/10.3934/MICROBIOL.2017.3.529

Breijyeh, Z., Jubeh, B., & Karaman, R. (2020). Resistance of Gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules(Basel)*, *25*(6), 1340. https://doi.org/10.3390/MOLECULES25061340

Briers, Y., Cornelissen, A., Aertsen, A., Hertveldt, K., Michiels, C. W., Volckaert, G., & Lavigne, R. (2008). Analysis of outer membrane permeability of *Pseudomonas aeruginosa* and bactericidal activity of endolysins KZ144 and EL188 under high hydrostatic pressure. *FEMS Microbiology Letters*, *280*(1), 113–119. https://doi.org/10.1111/J.1574-6968.2007.01051.X

Briers, Y., Schmelcher, M., Loessner, M. J., Hendrix, J., Engelborghs, Y., Volckaert, G., & Lavigne, R. (2009). The high-affinity peptidoglycan binding domain of *Pseudomonas* phage endolysin KZ144. *Biochemical and Biophysical Research Communications*, *383*(2), 187–191. https://doi.org/10.1016/J.BBRC.2009.03.161

Briers, Y., Walmagh, M., Van Puyenbroeck, V., Cornelissenm, A., Cenens, W., Aertsen, A., Oliveira, H., Azeredo, J., Verween, G., Pirnay, J. P., Miller, S., Volckaert, G., & Lavigne, R. (2014a). Engineered endolysin-based "Artilysins" to combat multidrug-resistant gram-negative pathogens. *mBio*, *5*(4), e01379–14. https://doi.org/10.1128/mBio.01379-14

Briers, Y., Walmagh, M., Grymonprez, B., Biebl, M., Pirnay, J. P., Defraine, V., Michiels, J., Cenens, W., Aertsen, A., Miller, S., & Lavigne, R. (2014b). Art-175 is a highly efficient antibacterial against multidrug-resistant strains and persisters of *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy*, *58*(7), 3774–3784. https://journals.asm.org/doi/10.1128/AAC.02668-14

Burmeister, A. R., Fortier, A., Roush, C., Lessing, A. J., Bender, R. G., Barahman, R., Grant, R., Chan, B. K., & Turner, P. E. (2020). Pleiotropy complicates a trade-off between phage resistance and antibiotic resistance. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(21), 11207–11216. https://doi.org/10.1073/PNAS.1919888117

Chang, Y. (2020). Bacteriophage-derived endolysins applied as potent biocontrol agents to enhance food safety. *Microorganisms*, *8*(5), 724. https://doi.org/10.3390/MICROORGANISMS8050724

Chinivasagam, H. N., Estella, W., Maddock, L., Mayer, D. G., Weyand, C., Connerton, P. L., & Connerton, I. F. (2020). Bacteriophages to control *Campylobacter* in commercially farmed broiler chickens, in Australia. *Frontiers in Microbiology*, *11*, 632. https://www.frontiersin.org/article/10.3389/fmicb.2020.00632

Clavijo, V., Baquero, D., Hernandez, S., Farfan, J. C., Arias, J., Arévalo, A., Donado-Godoy, P., & Vives-Flores, M. (2019). Phage cocktail SalmoFREE® reduces *Salmonella* on a commercial broiler farm. *Poultry Science*, *98*(10), 5054–5063. https://doi.org/10.3382/PS/PEZ251

Colom, J., Cano-Sarabia, M., Otero, J., Aríñez-Soriano, J., Cortés, P., Maspoch, D., & Llagostera, M. (2017). Microencapsulation with alginate/$CaCO_3$: A strategy for improved phage therapy. *Scientific Reports*, *7*, 41441. https://doi.org/10.1038/SREP41441

D'angelantonio, D., Scattolini, S., Boni, A., Neri, D., Di Serafino, G., Connerton, P., Connerton, I., Pomilio, F., Di Giannatale, E., Migliorati, G., & Aprea, G. (2021). Bacteriophage therapy to reduce colonization of *Campylobacter jejuni* in broiler chickens before slaughter. *Viruses*, *13*(8), 1428. https://doi.org/10.3390/V13081428

Defraine, V., Schuermans, J., Grymonprez, B., Govers, S. K., Aertsen, A., Fauvart, M., Michiels, J., Lavigne, R., & Briers, Y. (2016). Efficacy of artilysin art-175 against resistant and persistent *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, *60*(6), 3480–3488. https://doi.org/10.1128/AAC.00285-16

Delcour, A. H. (2009). Outer membrane permeability and antibiotic resistance. *Biochimica Et Biophysica Acta (BBA) - Proteins and Proteomics*, *1794*(5), 808–816. https://doi.org/10.1016/J.BBAPAP.2008.11.005

De Maesschalck, V., Gutiérrez, D., Paeshuyse, J., Lavigne, R., & Briers, Y. (2020). Advanced engineering of third-generation lysins and formulation strategies for clinical applications. *Critical Reviews in Microbiology*, *46*(5), 548–564. https://doi.org/10.1080/1040841X.2020.1809346

Ding, Y., Zhang, Y., Huang, C., Wang, J., & Wang, X. (2020). An endolysin LysSE24 by bacteriophage LPSE1 confers specific bactericidal activity against multidrug-resistant *Salmonella* strains. *Microorganisms*, *8*(5), 737. https://doi.org/10.3390/microorganisms8050737

Dong, H., Zhu, C., Chen, J., Ye, X., & Huang, Y. P. (2015). Antibacterial activity of *Stenotrophomonas maltophilia* endolysin P28 against both Gram-positive and Gram-negative bacteria. *Frontiers in Microbiology*, *6*, 1299. https://doi.org/10.3389/FMICB.2015.01299

Doron, S., Melamed, S., Ofir, G., Leavitt, A., Lopatina, A., Keren, M., Amitai, G., & Sorek, R. (2018). Systematic discovery of antiphage defense systems in the microbial pangenome. *Science*, *359*(6379), eaar4120. https://www.science.org/doi/10.1126/science.aar4120

Duc, H. M., Son, H. M., Honjoh, K.-I., & Miyamoto, T. (2018). Isolation and application of bacteriophages to reduce *Salmonella* contamination in raw chicken meat. *LWT - Food Science and Technology*, *91*, 353–360. https://doi.org/10.1016/J.LWT.2018.01.072

Duc, H. M., Son, H. M., Yi, H. P. S., Sato, J., Ngan, P. H., Masuda, Y., Honjoh, K.-I., & Miyamoto, T. (2020). Isolation, characterization and application of a polyvalent phage capable of controlling *Salmonella* and *Escherichia coli* O157:H7 in different food matrices. *Food Research International*, *131*, 108977. https://doi.org/10.1016/j.foodres.2020.108977

ECDC. (2022). https://www.ecdc.europa.eu/en/publications-data/yersiniosis-annual-epidemiological-report-2020

EFSA. (2021). https://www.efsa.europa.eu/en/news/campylobacter-and-salmonella-cases-stable-eu

Facciolà, A., Riso, R., Avventuroso, E., Visalli, G., Delia, S. A., & Laganà, P. (2017). *Campylobacter*: From microbiology to prevention. *Journal of Preventive Medicine and Hygiene*, *58*(2), E79–E92.

Filik, K., Szermer-Olearnik, B., Niedziółka-Jönson, J., Roźniecka, E., Ciekot, J., Pyra, A., Matyjaszczyk, I., Skurnik, M., & Brzozowska, E. (2022). φYeO3-12 phage tail fiber Gp17 as a promising high specific tool for recognition of *Yersinia enterocolitica* pathogenic serotype O:3. *AMB Express*, *12*(1), 1. https://doi.org/10.1186/S13568-021-01341-2

Fischetti, V. (2018). Development of phage lysins as novel therapeutics: A historical perspective. *Viruses*, *10*(6), 310. https://doi.org/10.3390/V10060310

Fister, S., Robben, C., Witte, A. K., Schoder, D., Wagner, M., & Rossmanith, P. (2016). Influence of environmental factors on phage-bacteria interaction and on the efficacy and infectivity of phage P100. *Frontiers in Microbiology*, *7*, 1152. https://doi.org/10.3389/fmicb.2016.01152

Fong, K., Wong, C. W. Y., Wang, S., & Delaquis, P. (2021). How broad is enough: The host range of bacteriophages and its impact on the agri-food sector. *Phage*, *2*(2), 83–91. https://doi.org/10.1089/PHAGE.2020.0036

García, P., Martínez, B., Obeso, J. M., & Rodríguez, A. (2008). Bacteriophages and their application in food safety. *Letters in Applied Microbiology*, *47*(6), 479–485. https://doi.org/10.1111/j.1472-765X.2008.02458.x

García, P., Martínez, B., Rodríguez, L., & Rodríguez, A. (2010b). Synergy between the phage endolysin LysH5 and nisin to kill *Staphylococcus aureus* in pasteurized milk. *International Journal of Food Microbiology*, *141*(3), 151–155. https://doi.org/10.1016/J.IJFOODMICRO.2010.04.029

García, P., Rodríguez, L., Rodríguez, A., & Martínez, B. (2010a). Food biopreservation: Promising strategies using bacteriocins, bacteriophages and endolysins. *Trends in Food Science and Technology*, *21*(8), 373–382. https://doi.org/10.1016/j.tifs.2010.04.010

Gerstmans, H., Gerstmans, H., Gerstmans, H., Grimon, D., Gutiérrez, D., Gutiérrez, D., Lood, C., Lood, C., Rodríguez, A., van Noort, V., van Noort, V., Lammertyn, J., Lavigne, R., & Briers, Y. (2020). A VersaTile-driven platform for rapid hit-to-lead development of engineered lysins. *Science Advances*, *6*(23), eaaz1136. https://www.science.org/doi/10.1126/sciadv.aaz1136

Giannella, R. A. (1996). *Salmonella*. In S. Baron (Ed.), Medical microbiology (4th ed.). *Galveston (TX): University of Texas Medical Branch at Galveston*. https://www.ncbi.nlm.nih.gov/books/NBK8435/

Giaouris, E., Heir, E., Desvaux, M., Hébraud, M., Møretrø, T., Langsrud, S., Doulgeraki, A., Nychas, G.-J., Kačániová, M., Czaczyk, K., Ölmez, H., & Simões, M. (2015). Intra- and inter-species interactions within biofilms of important foodborne bacterial pathogens. *Frontiers in Microbiology*, *6*, 841. https://doi.org/10.3389/FMICB.2015.00841

Gómez-Aldapa, C. A., Torres-Vitela, M. D. R., Villarruel-López, A., & Castro-Rosas, J. (2012). The role of foods in *Salmonella* infections. In B. S. M. Mahmoud (Eds.), *Salmonella - A dangerous foodborne pathogen*, IntechOpen. https://doi.org/10.5772/28316

Gomez-Garcia, J., Chavez-Carbajal, A., Segundo-Arizmendi, N., Baron-Pichardo, M. G., Mendoza-Elvira, S. E., Hernandez-Baltazar, E., Hynes, A. P., & Torres-Angeles, O. (2021). Efficacy of *Salmonella* bacteriophage s1 delivered and released by alginate beads in a chicken model of infection. *Viruses*, *13*(10), 1932. https://doi.org/10.3390/V13101932

Gondil, V. S., & Chhibber, S. (2021). Bacteriophage and endolysin encapsulation systems: A promising strategy to improve therapeutic outcomes. *Frontiers in Pharmacology*, *12*, 1113. https://doi.org/10.3389/FPHAR.2021.675440

Gong, B., Li, H., Feng, Y., Zeng, S., Zhuo, Z., Luo, J., Chen, X., & Li, X. (2022). Prevalence, serotype distribution and antimicrobial resistance of non-typhoidal *Salmonella* in hospitalized patients in Conghua District of Guangzhou, China. *Frontiers in Cellular and Infection Microbiology*, *12*, 54. https://doi.org/10.3389/FCIMB.2022.805384

Gorzkiewicz, M., Konopka, M., Janaszewska, A., Tarasenko, I. I., Sheveleva, N. N., Gajek, A., Neelov, I. M., & Klajnert-Maculewicz, B. (2020). Application of new lysine-based peptide dendrimers D3K2 and D3G2 for gene delivery: Specific cytotoxicity to cancer cells and transfection in vitro. *Bioorganic Chemistry*, *95*, 103504. https://doi.org/10.1016/J.BIOORG.2019.103504

Grabowski, Ł., Łepek, K., Stasiłojć, M., Kosznik-Kwaśnicka, K., Zdrojewska, K., Maciąg-Dorszyńska, M., Węgrzyn, G., & Węgrzyn, A. (2021). Bacteriophage-encoded enzymes destroying bacterial cell membranes and walls, and their potential use as antimicrobial agents. *Microbiological Research*, *248*, 126746. https://doi.org/10.1016/J.MICRES.2021.126746

Grant, A. Q., Parveen, S., Schwarz, J., Hashem, F., & Vimini, B. (2017). Reduction of *Salmonella* in ground chicken using a bacteriophage. *Poultry Science*, *96*(8), 2845–2852. https://doi.org/10.3382/PS/PEX062

Gray, J. A., Chandry, P. S., Kaur, M., Kocharunchitt, C., Bowman, J. P., & Fox, E. M. (2018). Novel biocontrol methods for *Listeria monocytogenes* biofilms in food production facilities. *Frontiers in Microbiology*, *9*, 605. https://doi.org/10.3389/fmicb.2018.00605

Gutiérrez, D., & Briers, Y. (2021). Lysins breaking down the walls of Gram-negative bacteria, no longer a no-go. *Current Opinion in Biotechnology*, *68*, 15–22. https://doi.org/10.1016/J.COPBIO.2020.08.014

Hagens, S., de Vegt, B., & Peterson, R. (2018). Efficacy of a commercial phage cocktail in reducing *Salmonella* contamination on poultry Products - Laboratory data and industrial trial data. *Meat and Muscle Biology*, *2*(2), 156. https://doi.org/10.1751/RMC2018.136

Hernando-Amado, S., Coque, T. M., Baquero, F., & Martínez, J. L. (2019). Defining and combating antibiotic resistance from One Health and Global Health perspectives. *Nature Microbiology*, *4*(9), 1432–1442. https://doi.org/10.1038/s41564-019-0503-9

Heselpoth, R. D., Euler, C. W., Schuch, R., & Fischetti, V. A. (2019). Lysocins: Bioengineered antimicrobials that deliver lysins across the outer membrane of Gram-negative bacteria. *Antimicrobial Agents and Chemotherapy*, *63*(6), e00342–19. https://doi.org/10.1128/AAC.00342-19

Huang, C., Shi, J., Ma, W., Li, Z., Wang, J., Li, J., & Wang, X. (2018). Isolation, characterization, and application of a novel specific *Salmonella* bacteriophage in different food matrices. *Food Research International*, *111*, 631–641. https://doi.org/10.1016/J.FOODRES.2018.05.071

Hunt, J. M. (2010). Shiga toxin–Producing *Escherichia coli* (STEC). *Clinics in Laboratory Medicine*, *30*(1), 21. https://doi.org/10.1016/J.CLL.2009.11.001

Ibarra-Sánchez, L. A., Van Tassell, M. L., & Miller, M. J. (2018). Antimicrobial behavior of phage endolysin PlyP100 and its synergy with nisin to control *Listeria monocytogenes* in Queso Fresco. *Food Microbiology*, *72*, 128–134. https://doi.org/10.1016/J.FM.2017.11.013

Islam, M. S., Hu, Y., Mizan, M. F. R., Yan, T., Nime, I., Zhou, Y., & Li, J. (2020a). Characterization of *Salmonella* phage LPST153 that effectively targets most prevalent *Salmonella* serovars. *Microorganisms*, *8*(7), 1089. https://doi.org/10.3390/MICROORGANISMS8071089

Islam, M. S., Zhou, Y., Liang, L., Nime, I., Liu, K., Yan, T., Wang, X., & Li, J. (2019). Application of a phage cocktail for control of *Salmonella* in foods and reducing biofilms. *Viruses*, *11*(9), 841. https://doi.org/10.3390/V11090841

Islam, M. S., Zhou, Y., Liang, L., Nime, I., Yan, T., Willias, S. P., Mia, M. Z., Bei, W., Connerton, I. F., Fischetti, V. A., & Li, J. (2020b). Application of a broad range lytic phage LPST94 for biological control of *Salmonella* in foods. *Microorganisms*, *8*(2), 247. https://doi.org/10.3390/MICROORGANISMS8020247

Jończyk, E., Kłak, M., Międzybrodzki, R., & Górski, A. (2011). The influence of external factors on bacteriophages—Review. *Folia Microbiologica*, *56*(3), 191. https://doi.org/10.1007/S12223-011-0039-8

Jun, J. W., Park, S. C., Wicklund, A., & Skurnik, M. (2018). Bacteriophages reduce *Yersinia enterocolitica* contamination of food and kitchenware. *International Journal of Food Microbiology*, *271*, 33–47. https://doi.org/10.1016/j.ijfoodmicro.2018.02.007

Kashani, H. H., Fahimi, H., Goli, Y. D., & Moniri, R. (2017). A novel chimeric endolysin with antibacterial activity against methicillin-resistant *Staphylococcus aureus*. *Frontiers in Cellular and Infection Microbiology*, *7*, 290. https://doi.org/10.3389/FCIMB.2017.00290

Kasman, L. M., & Porter, L. D. (2021). Bacteriophages. *Brenner's Encyclopedia of Genetics: Second Edition*, *2013*, 280–283. https://doi.org/10.1016/B978-0-12-374984-0.00131-5

Kaur, J., Kour, A., Panda, J. J., Harjai, K., & Chhibber, S. (2020). Exploring endolysin-loaded alginate-chitosan nanoparticles as future remedy for *Staphylococcal* infections. *AAPS PharmSciTech*, *21*(6), 233. https://doi.org/10.1208/S12249-020-01763-4

Kawacka, I., Olejnik-Schmidt, A., Schmidt, M., & Sip, A. (2020). Effectiveness of phage-based inhibition of *Listeria monocytogenes* in food products and food processing environments. *Microorganisms*, *8*(11), 1764. https://doi.org/10.3390/MICROORGANISMS8111764

Khawaja, K. A., Rauf, M., Abbas, Z., & Rehman, S. U. (2016). A virulent phage JHP against *Pseudomonas aeruginosa* showed infectivity against multiple genera. *Journal of Basic Microbiology*, *56*(10), 1090–1097. https://doi.org/10.1002/JOBM.201500764

Kim, J. H., Kim, H. J., Jung, S. J., Mizan, M. F. R., Park, S. H., & Ha, S.-D. (2020). Characterization of *Salmonella* spp.-specific bacteriophages and their biocontrol application in chicken breast meat. *Journal of Food Science*, *85*(3), 526–534. https://doi.org/10.1111/1750-3841.15042

Kim, S., Kim, S. H., Rahman, M., & Kim, J. (2018). Characterization of a *Salmonella enteritidis* bacteriophage showing broad lytic activity against Gram-negative enteric bacteria. *Journal of Microbiology*, *56*(12), 917–925. https://doi.org/10.1007/S12275-018-8310-1

Kocot, A. M., Wróblewska, B., & Cabo, M. L. (2021). Operational culture conditions determinate benzalkonium chloride resistance in *L. monocytogenes-E. coli* dual species biofilms. *International Journal of Food Microbiology*, *360*, 109441. https://doi.org/10.1016/J.IJFOODMICRO.2021.109441

Korzeniowski, P., Śliwka, P., Kuczkowski, M., Mišić, D., Milcarz, A., & Kuźmińska-Bajor, M. (2022). Bacteriophage cocktail can effectively control *Salmonella* biofilm in poultry housing. *Frontiers in Microbiology*, *13*, 2317. https://doi.org/10.3389/FMICB.2022.901770

Kosznik-Kwaśnicka, K., Podlacha, M., Grabowski, Ł., Stasiłojć, M., Nowak-Zaleska, A., Ciemińska, K., Cyske, Z., Dydecka, A., Gaffke, L., Mantej, J., Myślińska, D., Necel, A., Pierzynowska, K., Piotrowska, E., Radzanowska-Alenowicz, E., Rintz, E., Sitko, K., Topka-Bielecka, G., Węgrzyn, G., & Węgrzyn, A. (2022). Biological aspects of phage therapy versus antibiotics against *Salmonella enterica* serovar Typhimurium infection of chickens. *Frontiers in Cellular and Infection Microbiology*, *12*, 1105. https://doi.org/10.3389/FCIMB.2022.941867

Kovalskaya, N., Foster-Frey, J., Donovan, D. M., Bauchan, G., & Hammond, R. W. (2016). Antimicrobial activity of bacteriophage endolysin produced in *Nicotiana benthamiana* plants. *Journal of Microbiology and Biotechnology*, *26*(1), 160–170. https://doi.org/10.4014/JMB.1505.05060

Kuiper, J. W. P., Hogervorst, J. M. A., Herpers, B. L., Bakker, A. D., Klein-Nulend, J., Nolte, P. A., & Krom, B. P. (2021). The novel endolysin XZ.700 effectively treats MRSA biofilms in two biofilm models without showing toxicity on human bone cells in vitro. *Biofouling*, *37*(2), 184–193. https://doi.org/10.1080/08927014.2021.1887151

Legotsky, S. A., Vlasova, K. Y., Priyma, A. D., Shneider, M. M., Pugachev, V. G., Totmenina, O. D., Kabanov, A. V., Miroshnikov, K. A., & Klyachko, N. L. (2014). Peptidoglycan degrading activity of the broad-range *Salmonella* bacteriophage S-394 recombinant endolysin. *Biochimie*, *107*(PB), 293–299. https://doi.org/10.1016/J.BIOCHI.2014.09.017

Letrado, P., Corsini, B., DÍez-Martínez, R., Bustamante, N., Yuste, J. E., & García, P. (2018). Bactericidal synergism between antibiotics and phage endolysin Cpl-711 to kill multidrug-resistant pneumococcus. *Future Microbiology*, *13*(11), 1215–1223. https://doi.org/10.2217/FMB-2018-0077

Li, Y.-K., Chen, H., Shu, M., Zhong, C., Bi, Y., Yang, H.-H., & Wu, G.-P. (2021c). Isolation, characterization and application of an alkaline resistant virulent bacteriophage JN01 against *Escherichia coli* O157:H7 in milk and beef. *LWT*, *144*, 111266. https://doi.org/10.1016/j.lwt.2021.111266

Li, J., Li, Y., Ding, Y., Huang, C., Zhang, Y., Wang, J., & Wang, X. (2021a). Characterization of a novel *Siphoviridae Salmonella* bacteriophage T156 and its microencapsulation application in food matrix. *Food Research International*, *140*, 110004. https://doi.org/10.1016/J.FOODRES.2020.110004

Li, Z., Li, W., Ma, W., Ding, Y., Zhang, Y., Yang, Q., Wang, J., & Wang, X. (2021b). Characterization and application of a lytic phage D10 against multidrug-resistant *Salmonella*. *Viruses*, *13*(8), 1626. https://doi.org/10.3390/v13081626

Lim, J.-A., Shin, H., Heu, S., & Ryu, S. (2014). Exogenous lytic activity of SPN9CC endolysin against Gram-negative bacteria. *Journal of Microbiology and Biotechnology*, *24*(6), 803–811. https://doi.org/10.4014/JMB.1403.03035

Liu, A., Liu, Y., Peng, L., Cai, X., Shen, L., Duan, M., Ning, Y., Liu, S., Li, C., Liu, Y., Chen, H., Wu, W., Wang, X., Hu, B., & Li, C. (2020). Characterization of the narrow-spectrum bacteriophage LSE7621 towards *Salmonella enteritidis* and its biocontrol potential on lettuce and tofu. *LWT*, *118*, 108791.

Liu, A., Wang, Y., Cai, X., Jiang, S., Cai, X., Shen, L., Liu, Y., Han, G., Chen, S., Wang, J., Wu, W., Li, C., Liu, S., & Wang, X. (2019). Characterization of endolysins from bacteriophage LPST10 and evaluation of their potential for controlling *Salmonella* Typhimurium on lettuce. *LWT*, *114*, 108372. https://doi.org/10.1016/J.LWT.2019.108372

Loc-Carrillo, C., & Abedon, S. T. (2011). Pros and cons of phage therapy. *Bacteriophage*, *1*(2), 111. https://doi.org/10.4161/BACT.1.2.14590

Lukacik, P., Barnard, T. J., Keller, P. W., Chaturvedi, K. S., Seddiki, N., Fairman, J. W., Noinaj, N., Kirby, T. L., Henderson, J. P., Steven, B., A, C., Hinnebusch, J., & Buchanan, S. K. (2012). Structural engineering of a phage lysin that targets Gram-negative pathogens. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(25), 9857–9862. https://doi.org/10.1073/PNAS.1203472109

Lv, M., Wang, S., Yan, G., Sun, C., Feng, X., Gu, J., Han, W., & Lei, L. (2015). Genome sequencing and analysis of an *Escherichia coli* phage vB_EcoM-ep3 with a novel lysin, Lysep3. *Virus Genes*, *50*(3), 487–497. https://doi.org/10.1007/S11262-015-1195-8/FIGURES/12

Ma, Q., Guo, Z., Gao, C., Zhu, R., Wang, S., Yu, L., Qin, W., Xia, X., Gu, J., Yan, G., & Lei, L. (2016). Enhancement of the direct antimicrobial activity of Lysep3 against *Escherichia coli* by inserting cationic peptides into its C terminus. *Antonie Van Leeuwenhoek*, *110*(3), 347–355. https://doi.org/10.1007/S10482-016-0806-2

Mangieri, N., Picozzi, C., Cocuzzi, R., & Foschino, R. (2020). Evaluation of a potential bacteriophage cocktail for the control of Shiga-toxin producing *Escherichia coli* in food. *Frontiers in Microbiology*, *11*, 1801. https://doi.org/10.3389/FMICB.2020.01801

Markowicz-Piasecka, M., & Mikiciuk-Olasik, E. (2016). Dendrimers in drug delivery. *Nanobiomaterials in Drug Delivery*, *2016*, 39–74. https://doi.org/10.1016/B978-0-323-42866-8.00002-2

Millman, A., Bernheim, A., Stokar-Avihail, A., Fedorenko, T., Voichek, M., Leavitt, A., Oppenheimer-Shaanan, Y., & Sorek, R. (2020). Bacterial retrons function in anti-phage defense. *Cell*, *183*(6), 1551–1561.e12. https://doi.org/10.1016/J.CELL.2020.09.065

Misiou, O., Van Nassau, T. J., Lenz, C. A., & Vogel, R. F. (2018). The preservation of *Listeria*-critical foods by a combination of endolysin and high hydrostatic pressure. *International Journal of Food Microbiology*, *266*, 355–362. https://doi.org/10.1016/J.IJFOODMICRO.2017.10.004

Moulton-Brown, C. E., & Friman, V.-P. (2018). Rapid evolution of generalized resistance mechanisms can constrain the efficacy of phage–antibiotic treatments. *Evolutionary Applications*, *11*(9), 1630. https://doi.org/10.1111/EVA.12653

Moye, Z., Woolston, J., & Sulakvelidze, A. (2018). Bacteriophage applications for food production and processing. *Viruses*, *10*(4), 205. https://doi.org/10.3390/V10040205

Mukhopadhyay, S., & Gorris, L. G. M. (2014). Hurdle technology. *Encyclopedia of Food Microbiology: Second Edition*, *2014*, 221–227. https://doi.org/10.1016/B978-0-12-384730-0.00166-X

Murray, E., Draper, L. A., Ross, R. P., & Hill, C. (2021). The advantages and challenges of using endolysins in a clinical setting. *Viruses*, *13*(4), 680. https://doi.org/10.3390/V13040680

Nale, J. Y., Vinner, G. K., Lopez, V. C., Thanki, A. M., Phothaworn, P., Thiennimitr, P., Garcia, A., AbuOun, M., Anjum, M. F., Korbsrisate, S., Galyov, E. E., Malik, D. J., & Clokie, M. R. J. (2021). An optimized bacteriophage cocktail can effectively control *Salmonella* in vitro and in *Galleria mellonella*. *Frontiers in Microbiology*, *11*, 3370. https://doi.org/10.3389/FMICB.2020.609955

Nelson, D., Loomis, L., & Fischetti, V. A. (2001). Prevention and elimination of upper respiratory colonization of mice by group A streptococci by using a bacteriophage lytic enzyme. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(7), 4107–4112. https://doi.org/10.1073/PNAS.061038398

Niculescu, A.-G., & Grumezescu, A. M. (2022). Applications of chitosan-alginate-based nanoparticles—An up-to-date review. *Nanomaterials*, *12*(2), 186. https://doi.org/10.3390/NANO12020186

Nikaido, H. (2003). Molecular basis of bacterial outer membrane permeability revisited. *Microbiology and Molecular Biology Reviews*, *67*(4), 593–656. https://doi.org/10.1128/MMBR.67.4.593-656.2003

Ning, H., Zhang, J., Wang, Y., Lin, H., & Wang, J. (2023). Development of highly efficient artilysins against *Vibrio parahaemolyticus* via virtual screening assisted by molecular docking. *Food Control*, *146*, 109521. https://doi.org/10.1016/J.FOODCONT.2022.109521

Ofir, G., & Sorek, R. (2018). Contemporary phage biology: From classic models to new insights. *Cell*, *172*(6), 1260–1270. https://doi.org/10.1016/J.CELL.2017.10.045

Oliveira, H., Azeredo, J., Lavigne, R., & Kluskens, L. D. (2012). Bacteriophage endolysins as a response to emerging foodborne pathogens. *Trends in Food Science & Technology*, *28*(2), 103–115. https://doi.org/10.1016/J.TIFS.2012.06.016

Oliveira, H., São-José, C., & Azeredo, J. (2018). Phage-derived peptidoglycan degrading enzymes: Challenges and future prospects for in vivo therapy. *Viruses*, *10*(6), 292. https://doi.org/10.3390/V10060292

Oliveira, H., Thiagarajan, V., Walmagh, M., Sillankorva, S., Lavigne, R., Neves-Petersen, M. T., Kluskens, L. D., & Azeredo, J. (2014). A thermostable *Salmonella* phage endolysin, Lys68, with broad bactericidal properties against Gram-negative pathogens in presence of weak acids. *PLoS ONE*, *9*(10), e108376. https://doi.org/10.1371/JOURNAL.PONE.0108376

Park, H., Kim, J., Kim, M., Park, Y., & Ryu, S. (2021). Development of new strategy combining heat treatment and phage cocktail for post-contamination prevention. *Food Research International*, *145*, 110415. https://doi.org/10.1016/J.FOODRES.2021.110415

Park, D. W., Lim, G. Y., Lee, Y. D., & Park, J. H. (2020). Characteristics of lytic phage vB_EcoM-ECP26 and reduction of shiga-toxin producing *Escherichia coli* on produce romaine. *Applied Biological Chemistry*, *63*(1), 1–9. https://doi.org/10.1186/S13765-020-00502-4

Paule, A., Frezza, D., & Edeas, M. (2018). Microbiota and phage therapy: Future challenges in medicine. *Medical Sciences*, *6*(4), 86. https://doi.org/10.3390/MEDSCI6040086

Pereira, C., Moreirinha, C., Teles, L., Rocha, R. J. M., Calado, R., Romalde, J. L., Nunes, M. L., & Almeida, A. (2017). Application of phage therapy during bivalve depuration improves *Escherichia coli* decontamination. *Food Microbiology*, *61*, 102–112. https://doi.org/10.1016/J.FM.2016.09.003

Pirnay, J.-P., & Kutter, E. (2021). Bacteriophages: It's a medicine, Jim, but not as we know it. *The Lancet Infectious Diseases*, *21*(3), 309–311. https://doi.org/10.1016/S1473-3099(20)30464-3

Połaska, M., & Sokołowska, B. (2019). Bacteriophages—A new hope or a huge problem in the food industry. *AIMS Microbiology*, *5*(4), 324. https://doi.org/10.3934/MICROBIOL.2019.4.324

Popova, E., Khamidova, D., Neelov, I., & Komilov, F. (2017). Lysine dendrimers and their complexes with therapeutic and amyloid peptides: Computer simulation. In C. M. Simonescu (Ed.), *Dendrimers: Fundamentals and applications*. IntechOpen. https://doi.org/10.5772/INTECHOPEN.71052

Quintana-Sanchez, S., Gómez-Casanova, N., Sánchez-Nieves, J., Gómez, R., Rachuna, J., Wąsik, S., Semaniak, J., Maciejewska, B., Drulis-Kawa, Z., Ciepluch, K., Mata, F. J. D. L., & Arabski, M. (2022). The antibacterial effect of PEGylated carbosilane dendrimers on *P. aeruginosa* alone and in combination with phage-derived endolysin. *International Journal of Molecular Sciences*, *23*(3), 1873. https://doi.org/10.3390/IJMS23031873

Ricci, A., Allende, A., Bolton, D., Chemaly, M., Davies, R., Fernández Escámez, P. S., Girones, R., Herman, L., Koutsoumanis, K., Lindqvist, R., Robertson, L., Ru, G., Sanaa, M., Simmons, M., Skandamis, P., Snary, E., Speybroeck, N., Ter Kuile, B., Threlfall, J., … Nørrung, B. (2017). Guidance on the requirements for the development of microbiological criteria. *EFSA Journal*, *15*(11), e05052. https://doi.org/10.2903/J.EFSA.2017.5052

Richards, P. J., Connerton, P. L., & Connerton, I. F. (2019). Phage biocontrol of *Campylobacter jejuni* in chickens does not produce collateral effects on the gut microbiota. *Frontiers in Microbiology*, *10*, 476. https://doi.org/10.3389/FMICB.2019.00476

Sabtu, N., Enoch, D. A., & Brown, N. M. (2015). Antibiotic resistance: What, why, where, when and how? *British Medical Bulletin*, *116*, 105–113. https://doi.org/10.1093/bmb/ldv041

Schirmeier, E., Zimmermann, P., Hofmann, V., Biebl, M., Gerstmans, H., Maervoet, V. E. T., & Briers, Y. (2018). Inhibitory and bactericidal effect of Artilysin® Art-175 against colistin-resistant mcr-1-positive *Escherichia coli* isolates. *International Journal of Antimicrobial Agents*, *51*(3), 528–529. https://doi.org/10.1016/J.IJANTIMICAG.2017.08.027

Schmelcher, M., Donovan, D. M., & Loessner, M. J. (2012). Bacteriophage endolysins as novel antimicrobials. *Future Microbiology*, *7*(10), 1147–1171. https://doi.org/10.2217/FMB.12.97

Schmelcher, M., & Loessner, M. J. (2016). Bacteriophage endolysins: Applications for food safety. *Current Opinion in Biotechnology*, *37*, 76–87. https://doi.org/10.1016/j.copbio.2015.10.005

Shahin, K., & Bouzari, M. (2017). Bacteriophage application for biocontrolling *Shigella flexneri* in contaminated foods. *Journal of Food Science and Technology*, *55*(2), 550–559. https://doi.org/10.1007/S13197-017-2964-2

Shebs, E. L., Lukov, M. J., Giotto, F. M., Torres, E. S., & De Mello, A. S. (2020). Efficacy of bacteriophage and organic acids in decreasing STEC O157:H7 populations in beef kept under vacuum and aerobic conditions: A simulated High Event Period scenario. *Meat Science*, *162*, 108023. https://doi.org/10.1016/j.meatsci.2019.108023

Shen, K.-S., Shu, M., Tang, M.-X., Yang, W.-Y., Wang, S.-C., Zhong, C., & Wu, G.-P. (2022). Molecular cloning, expression and characterization of a bacteriophage JN01 endolysin and its antibacterial activity against *E. coli* O157:H7. *LWT*, *165*, 113705. https://doi.org/10.1016/J.LWT.2022.113705

Sheveleva, N. N., Markelov, D. A., Vovk, M. A., Mikhailova, M. E., Tarasenko, I. I., Tolstoy, P. M., Neelov, I. M., & Lähderanta, E. (2019). Lysine-based dendrimer with double arginine residues. *RSC Advances*, *9*(31), 18018–18026. https://doi.org/10.1039/C9RA02461A

Soffer, N., Woolston, J., Li, M., Das, C., & Sulakvelidze, A. (2017). Bacteriophage preparation lytic for *Shigella* significantly reduces *Shigella sonnei* contamination in various foods. *PLoS ONE*, *12*(3), e0175256. https://doi.org/10.1371/JOURNAL.PONE.0175256

Son, H. M., Duc, H. M., Masuda, Y., Honjoh, K. I., & Miyamoto, T. (2018). Application of bacteriophages in simultaneously controlling *Escherichia coli* O157:H7 and extended-spectrum beta-lactamase producing *Escherichia coli*. *Applied Microbiology and Biotechnology*, *102*(23), 10259–10271. https://doi.org/10.1007/S00253-018-9399-1

Sonalika, J., Srujana, A. S., Akhila, D. S., Juliet, M. R., & Santhosh, K. S. (2020). Application of bacteriophages to control *Salmonella* Enteritidis in raw eggs. *Iranian Journal of Veterinary Research*, *21*(3), 221–225. https://doi.org/10.22099/IJVR.2020.36349.5307

Soto, M. J., Retamales, J., Palza, H., & Bastías, R. (2018). Encapsulation of specific *Salmonella* Enteritidis phage f3αSE on alginate-spheres as a method for protection and dosification. *Electronic Journal of Biotechnology*, *31*, 57–60. https://doi.org/10.1016/J.EJBT.2017.11.006

Starkevič, U., Bortesi, L., Virgailis, M., Ružauskas, M., Giritch, A., & Ražanskienė, A. (2015). High-yield production of a

functional bacteriophage lysin with antipneumococcal activity using a plant virus-based expression system. *Journal of Biotechnology*, *200*, 10–16. https://doi.org/10.1016/J.JBIOTEC.2015.02.028

Stoffels, L., Taunt, H. N., Charalambous, B., & Purton, S. (2017). Synthesis of bacteriophage lytic proteins against *Streptococcus pneumoniae* in the chloroplast of *Chlamydomonas reinhardtii*. *Plant Biotechnology Journal*, *15*(9), 1130–1140. https://doi.org/10.1111/PBI.12703

Sulakvelidze, A., Alavidze, Z., & Morris, J. (2001). Bacteriophage therapy. *Antimicrobial Agents and Chemotherapy*, *45*(3), 649–659. https://doi.org/10.1128/AAC.45.3.649-659.2001

Szadkowska, M., Olewniczak, M., Kloska, A., Jankowska, E., Kapusta, M., Rybak, B., Wyrzykowski, D., Zmudzinska, W., Gieldon, A., Kocot, A., Kaczorowska, A.-K., Nierzwicki, L., Makowska, J., Kaczorowski, T., & Plotka, M. (2022). A novel cryptic clostridial peptide that kills bacteria by a cell membrane permeabilization mechanism. *Microbiology Spectrum*, *10*(5), e01657–22. https://doi.org/10.1128/SPECTRUM.01657-22

Tanaka, C., Yamada, K., Takeuchi, H., Inokuchi, Y., Kashiwagi, A., & Toba, T. (2018). A lytic bacteriophage for controlling *Pseudomonas lactis* in raw cow's milk. *Applied and Environmental Microbiology*, *84*(18), e00111–18. https://doi.org/10.1128/AEM.00111-18

Terajima, J., Izumiya, H., Hara-Kudo, Y., & Ohnishi, M. (2017). Shiga toxin (Verotoxin)-producing *Escherichia coli* and foodborne disease: A review. *Food Safety*, *5*(2), 35. https://doi.org/10.14252/FOODSAFETYFSCJ.2016029

Thanki, A. M., Mignard, G., Atterbury, R. J., Barrow, P., Millard, A. D., & Clokie, M. R. J. (2022). Prophylactic delivery of a bacteriophage cocktail in feed significantly reduces *Salmonella* colonization in pigs. *Microbiology Spectrum*, *10*(3), e00422–22. https://doi.org/10.1128/SPECTRUM.00422-22

Thornval, N. R., & Hoorfar, J. (2021). Progress in detection of *Campylobacter* in the food production chain. *Current Opinion in Food Science*, *39*, 16–21. https://doi.org/10.1016/J.COFS.2020.12.001

Thung, T. Y., Premarathne, J. M. K. J. K., San Chang, W., Loo, Y. Y., Chin, Y. Z., Kuan, C. H., Tan, C. W., Basri, D. F., Radzi, C. W. J. W. M., & Radu, S. (2017). Use of a lytic bacteriophage to control *Salmonella* Enteritidis in retail food. *LWT*, *78*, 222–225. https://doi.org/10.1016/J.LWT.2016.12.044

Tolen, T., Xie, Y., Hairgrove, T., Gill, J., & Taylor, T. (2018). Evaluation of commercial prototype bacteriophage intervention designed for reducing O157 and Non-O157 Shiga-toxigenic *Escherichia coli* (STEC) on beef cattle hide. *Foods*, *7*(7), 114. https://doi.org/10.3390/FOODS7070114

Tomat, D., Casabonne, C., Aquili, V., Balagué, C., & Quiberoni, A. (2018). Evaluation of a novel cocktail of six lytic bacteriophages against Shiga toxin-producing *Escherichia coli* in broth, milk and meat. *Food Microbiology*, *76*, 434–442. https://doi.org/10.1016/J.FM.2018.07.006

Ukuku, D. O., & Bari, M. L. (2022). Yersinia enterocolitica. In M. P. Doyle, F. Diez-Gonzalez, & C. Hill (Eds.), *Food microbiology: Fundamentals and frontiers* (pp. 437–450). Wiley. https://doi.org/10.1128/9781555819972.ch16

van Nieuwenhuyse, B., van der Linden, D., Chatzis, O., Lood, C., Wagemans, J., Lavigne, R., de Magnee, C., Sokal, E., Rodriguez-Villalobos, H., Djebara, S., Soentjens, P., & Pirnay, J.-P. (2022). Phage therapy to allow liver transplantation in a toddler infected by an extensively drug-resistant *Pseudomonas aeruginosa*. http://hdl.handle.net/2078.1/259871

Vaz, C. S. L., Voss-Rech, D., Alves, L., Coldebella, A., Brentano, L., & Trevisol, I. M. (2020). Effect of time of therapy with wild-type lytic bacteriophages on the reduction of *Salmonella* Enteritidis in broiler chickens. *Veterinary Microbiology*, *240*, 108527. https://doi.org/10.1016/J.VETMIC.2019.108527

Vázquez, R., Blanco-Gañán, S., Ruiz, S., & García, P. (2021). Mining of Gram-negative surface-active enzybiotic candidates by sequence-based calculation of physicochemical properties. *Frontiers in Microbiology*, *12*, 1009. https://doi.org/10.3389/FMICB.2021.660403

Vikram, A., Callahan, M. T., Woolston, J. W., Sharma, M., & Sulakvelidze, A. (2022). Phage biocontrol for reducing bacterial foodborne pathogens in produce and other foods. *Current Opinion in Biotechnology*, *78*, 102805. https://doi.org/10.1016/J.COPBIO.2022.102805

Vikram, A., Tokman, J. I., Woolston, J., & Sulakvelidze, A. (2020b). Phage biocontrol improves food safety by significantly reducing the level and prevalence of *Escherichia coli* O157:H7 in various foods. *Journal of Food Protection*, *83*(4), 668–676. https://doi.org/10.4315/0362-028X.JFP-19-433

Vikram, A., Woolston, J., & Sulakvelidze, A. (2020a). Phage biocontrol applications in food production and processing. *Current Issues in Molecular Biology*, *40*, 267–302. https://doi.org/10.21775/CIMB.040.267

Vinner, G. K., & Malik, D. J. (2018). High precision microfluidic microencapsulation of bacteriophages for enteric delivery. *Research in Microbiology*, *169*(9), 522–530. https://doi.org/10.1016/J.RESMIC.2018.05.011

Vinner, G. K., Richards, K., Leppanen, M., Sagona, A. P., & Malik, D. J. (2019). Microencapsulation of enteric bacteriophages in a pH-responsive solid oral dosage formulation using a scalable membrane emulsification process. *Pharmaceutics*, *11*(9), 475. https://doi.org/10.3390/PHARMACEUTICS11090475

Walmagh, M., Briers, Y., Santos, S. B. D., Azeredo, J., & Lavigne, R. (2012). Characterization of modular bacteriophage endolysins from *Myoviridae* phages OBP, 201φ2-1 and PVP-SE1. *PLoS ONE*, *7*(5), e36991. https://doi.org/10.1371/JOURNAL.PONE.0036991

Wang, M., Liu, P., Zhou, Q., Tao, W., Sun, Y., & Zeng, Z. (2018). Estimating the contribution of bacteriophage to the dissemination of antibiotic resistance genes in pig feces. *Environmental Pollution*, *238*, 291–298. https://doi.org/10.1016/j.envpol.2018.03.024

WHO. (2022). https://www.who.int/news-room/fact-sheets/detail/food-safety

Wienhold, S.-M., Lienau, J., & Witzenrath, M. (2019). Towards inhaled phage therapy in Western Europe. *Viruses*, *11*(3), 295. https://doi.org/10.3390/V11030295

Wójcik, E. A., Stańczyk, M., Wojtasik, A., Kowalska, J. D., Nowakowska, M., Łukasiak, M., Bartnicka, M., Kazimierczak, J., & Dastych, J. (2020). Comprehensive evaluation of the safety and efficacy of BAFASAL® bacteriophage preparation for the reduction of *Salmonella* in the food chain. *Viruses*, *12*(7), 742. https://doi.org/10.3390/V12070742

Wong, C. W. Y., Delaquis, P., Goodridge, L., Lévesque, R. C., Fong, K., & Wang, S. (2020). Inactivation of *Salmonella enterica* on postharvest cantaloupe and lettuce by a lytic bacteriophage cocktail. *Current Research in Food Science*, *2*, 25–32. https://doi.org/10.1016/J.CRFS.2019.11.004

Xu, Y. (2021a). Phage and phage lysins: New era of bio-preservatives and food safety agents. *Journal of Food Science*, *86*(8), 3349–3373. https://doi.org/10.1111/1750-3841.15843

Xu, S., Campisi, E., Li, J., & Fischetti, V. A. (2021b). Decontamination of *Escherichia coli* O157:H7 on fresh Romaine lettuce using a novel bacteriophage lysin. *International Journal of Food Microbiology*, *341*, 109068. https://doi.org/10.1016/J.IJFOODMICRO.2021.109068

Yamaki, S., Yamazaki, K., & Kawai, Y. (2022). Broad host range bacteriophage, EscoHU1, infecting *Escherichia coli* O157:H7 and *Salmonella enterica*: Characterization, comparative genomics, and applications in food safety. *International Journal of Food Microbiology*, *372*, 109680. https://doi.org/10.1016/J.IJFOODMICRO.2022.109680

Yan, T., Liang, L., Yin, P., Zhou, Y., Sharoba, A. M., Lu, Q., Dong, X., Liu, K., Connerton, I. F., & Li, J. (2020). Application of a novel phage LPSEYT for biological control of *Salmonella* in foods. *Microorganisms*, *8*(3), 400. https://doi.org/10.3390/MICROORGANISMS8030400

Yan, G., Liu, J., Ma, Q., Zhu, R., Guo, Z., Gao, C., Wang, S., Yu, L., Gu, J., Hu, D., Han, W., Du, R., Yang, J., & Lei, L. (2017). The N-terminal and central domain of colicin A enables phage lysin to lyse *Escherichia coli* extracellularly. *Antonie van Leeuwenhoek*, *110*(12), 1627–1635. https://doi.org/10.1007/S10482-017-0912-9

Yang, H., Wang, M., Yu, J., & Wei, H. (2015). Antibacterial activity of a novel peptide-modified lysin against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Frontiers in Microbiology*, *6*, 1471. https://doi.org/10.3389/FMICB.2015.01471

Yang, Y., Xie, X., Tang, M., Liu, J., Tuo, H., Gu, J., Tang, Y., Lei, C., Wang, H., & Zhang, A. (2020). Exploring the profile of antimicrobial resistance genes harboring by bacteriophage in chicken feces. *Science of the Total Environment*, *700*, 134446. https://doi.org/10.1016/j.scitotenv.2019.134446

Yeh, Y., De Moura, F. H., Van Den Broek, K., & De Mello, A. S. (2018). Effect of ultraviolet light, organic acids, and bacteriophage on *Salmonella* populations in ground beef. *Meat Science*, *139*, 44–48. https://doi.org/10.1016/J.MEATSCI.2018.01.007

Zajančkauskaitė, A., Noreika, A., Rutkienė, R., Meškys, R., & Kaliniene, L. (2021). Low-temperature virus vB_EcoM_VR26 shows potential in biocontrol of STEC O26:H11. *Foods*, *10*(7), 1500. https://doi.org/10.3390/FOODS10071500

Zampara, A., Sørensen, M. C. H., Gencay, Y. E., Grimon, D., Kristiansen, S. H., Jørgensen, L. S., Kristensen, J. R., Briers, Y., Elsser-Gravesen, A., & Brøndsted, L. (2021). Developing innolysins against *Campylobacter jejuni* using a novel prophage receptor-binding protein. *Frontiers in Microbiology*, *12*, 619028. https://doi.org/10.3389/FMICB.2021.619028

Zampara, A., Sørensen, M. C. H., Grimon, D., Antenucci, F., Briers, Y., & Brøndsted, L. (2018). Innolysins: A novel approach to engineer endolysins to kill Gram-negative bacteria. *BioRxiv*, *408948*, https://doi.org/10.1101/408948

Zampara, A., Sørensen, M. C. H., Grimon, D., Antenucci, F., Vitt, A. R., Bortolaia, V., Briers, Y., & Brøndsted, L. (2020). Exploiting phage receptor binding proteins to enable endolysins to kill Gram-negative bacteria. *Scientific Reports*, *10*(1), 1–12. https://doi.org/10.1038/s41598-020-68983-3

Zhang, Y., Ding, Y., Li, W., Zhu, W., Wang, J., & Wang, X. (2021b). Application of a novel lytic podoviridae phage Pu20 for biological control of drug-resistant *Salmonella* in liquid eggs. *Pathogens*, *10*(1), 34. https://doi.org/10.3390/pathogens10010034

Zhang, Y., Huang, H.-H., Duc, H. M., Masuda, Y., Honjoh, K.-I., & Miyamoto, T. (2021a). Endolysin LysSTG2: Characterization and application to control *Salmonella* Typhimurium biofilm alone and in combination with slightly acidic hypochlorous water. *Food Microbiology*, *98*, 103791. https://doi.org/10.1016/J.FM.2021.103791

Zhang, X., Niu, Y. D., Nan, Y., Stanford, K., Holley, R., Mcallister, T., & Narváez-Bravo, C. (2019). SalmoFresh™ effectiveness in controlling *Salmonella* on romaine lettuce, mung bean sprouts and seeds. *International Journal of Food Microbiology*, *305*, 108250. https://doi.org/10.1016/J.IJFOODMICRO.2019.108250

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