**Abstract:** Presently, biopreservation through protective bacterial cultures and their antimicrobial products or using antibacterial compounds derived from plants are proposed as feasible strategies to maintain the long shelf-life of products. Another emerging category of food biopreservatives are bacteriophages or their antibacterial enzymes called “phage lysins” or “enzybiotics”, which can be used directly as antibacterial agents due to their ability to act on the membranes of bacteria and destroy them. Bacteriophages are an alternative to antimicrobials in the fight against bacteria, mainly because they have a practically unique host range that gives them great specificity. In addition to their potential ability to specifically control strains of pathogenic bacteria, their use does not generate a negative environmental impact as in the case of antibiotics. Both phages and their enzymes can favor a reduction in antibiotic use, which is desirable given the alarming increase in resistance to antibiotics used not only in human medicine but also in veterinary medicine, agriculture, and in general all processes of manufacturing, preservation, and distribution of food. We present here an overview of the scientific background of phages and enzybiotics in the food industry, as well as food applications of these biopreservatives.

**Keywords:** bacteriophage; endolysin; enzybiotics; biopreservation

1. Introduction

Food preservation by suitable means is key in food safety and quality. There are several traditional and well-known physical preservation techniques such as refrigeration and pasteurization, but the modern industry is always looking for new procedures for food preservation to increase the product’s shelf-life by minimizing the loss of nutritional quality and organoleptic properties. Presently, some modern biopreservation techniques rely on naturally occurring microorganisms (i.e., lactic acid bacteria) and their metabolites. These food preservatives are mainly used to produce safer food for the consumer, preventing the action of pernicious microbes which can cause food deterioration or even toxicity and therefore be dangerous to human health.

Moreover, bacteria -including multidrug-resistant bacteria- can reach food at different points in the food supply chain, from farm to postharvest, and processing such as slaughtering, fermentation, packaging and storage [1–5].

As most natural foods are highly perishable, by extending their half-life we can also control their native microbiota for proper preservation, maintaining their safety and quality.
As microorganisms produce a long list of molecules ranging from classic antibiotics to antibacterial enzymes, the control of indigenous populations in food can be achieved by adding these products directly. The paradigm of bacterial molecules used in the food industry as biopreservatives is Nisin, a bacteriocin produced by the Gram-positive bacterium *Lactococcus lactis*, one of the lactic acid bacteria most extensively used for the manufacture of dairy products [6]. Other well-known bacteriocins, such as Pediocin, Natamycin, Enterocin, and Leucocin [7], also have inhibitory properties against other microorganisms which makes them very interesting for use in the food industry. Some bacteria that produce these compounds have been used as probiotics. Current research on probiotics is quite promising and modern fashion trends push probiotics and bacteriocins from modulation of the gut microbiota toward a wide range of other health-promoting activities away from food, such as cancer treatment, skin health care, periodontal health, or allergies [8–11].

In addition, the use of bacteriocin producing strains or those that can compete against pathogens in the context of the food industry needs new approaches, mainly due to the increase in foodborne infections, the appearance of new production processes, the massive demand for food, and the changing consumer trends. Moreover, the extensive use of antibiotics against animal and human pathogens has also led to an increase in foodborne pathogens resistant to antibiotics, which makes the picture not reassuring at all [12–14].

Goodridge and Abedon published an article in 2003 where they proposed to use the terms “phage biocontrol” and “phage bioprocessing” to differentiate the application of bacteriophages in the farm or crops from their use in the food industry [15]. Several years later, Greer published a review of the control of foodborne bacteria using phages, including the effects of these microorganisms on food storage and preservation [16].

At that time, the excellent properties of endolysins to kill bacteria were already known, but their use to protect food from foodborne pathogens had not yet been effectively tested. One of the first murein hydrolases to be studied concerning food-related bacteria was that of the *Lactobacillus helveticus* bacteriophage 0303 [17]. This endolysin exhibited a broad spectrum of activity, killing different bacterial species such *Pediococcus acidilactici, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus delbrueckii* subsp. *lactis, Lactobacillus acidophilus, Bacillus subtilis, Enterococcus faecium*, and several strains of *Lactobacillus helveticus*.

Problems of deterioration of the organoleptic properties have been described after physical treatments; also, consumers are increasingly demanding low-processed foods. One of the advantages of phages over the usual physical treatments is that phages do not modify any organoleptic properties of foods. Moreover, even with common treatments such as heat, team and UV light, a relatively high percentage of food products are lost due to subsequent microbial spoilage or microbial contamination; when food becomes contaminated, it will lead to food spoilage, and such food will no longer be fit for consumption.

Thanks to their ability to control or to inactivate spoilage and/or foodborne bacteria selectively, bacteriophages have great potential as food biopreservatives. Additionally, in terms of food biopreservation, enzybiotics are beginning to be increasingly studied in the field of food microbiology, taking advantage of the pull that in vitro successes have displayed against very important multidrug-resistant human and animal pathogens [18–20].

In this review, we discuss the use of phages and their lytic enzymes as a tool to eliminate or reduce spoilage bacteria and common foodborne bacterial pathogens.

2. Why Bacteriophages?

Bacteriophages are an alternative to antimicrobials in the fight against bacteria, mainly because they have a practically unique host range, which gives them great specificity. Apart from their selective activity, bacteriophages have been successfully tested to eliminate or weaken biofilms formed by different classes of both Gram-negative and Gram-positive pathogens in the food industry [21–24]. Biofilms are consortia of bacteria that persist on different surfaces or pipelines within the food industries that contaminate food at some point in the processing or packaging chain.
In addition to their potential ability to specifically control strains and biofilms of pathogenic bacteria, their use does not generate a negative environmental impact like in the case of antibiotics or disinfectants [25]. Other advantages of these viruses are: (i) safety—as they are not toxic to eukaryotic cells, (ii) the preservation of the organoleptic properties of food, and (iii) the control of multi-resistant bacteria since the tolerance of some strains to phages can often be overcome with the use of phage cocktails [14]. In addition, phages can be used in combination with antibiotics, bacteriocins, or even with probiotics.

The main limitations of bacteriophages as biopreservative tools in foods derive from the scarce knowledge of their genetics since the use of strains that may contain virulence factors, lysogeny, or antibiotic resistance genes is inadvisable. As an example, studies prior to this decade did not have the modern and inexpensive sequencing techniques that almost all laboratories can afford today. Furthermore, in some cases, it is necessary to use phage cocktails that are more difficult to characterize than individual strains. Additionally, we need to learn much more about their behavior within solid and liquid food matrices to optimize the amount of phage to be used in each case. The method of releasing phages on food is also important, since the phages must reach the largest number of bacteria possible so that they can effectively control them and reduce their number to safe values. In other words, phages and bacteria must be in contact with liquid but also with solid foods; moreover, as much bacterial contamination occurs initially at low numbers (a minimum bacterial density is a prerequisite) sometimes we must apply a large number of phages to those foods. Knowing the optimal number of viral particles (multiplicity of infection, MOI) to use for each food, as well as their infection kinetics in each food matrix, it is essential to understand how these phages are acting on their target pathogens [26–32]. Minimum host threshold requirement has been demonstrated for phages of different food pathogens [33,34]. As successful biopreservative agents, it is also important to consider phages’ stability in food matrices under different environmental conditions such as water activity, salinity, temperature, pH, osmotic shock, and light (visible and UV). According to several authors, phages have a remarkable stability in foods [35–37]. Phage propagation on a susceptible host, purification, and phage or cocktail formulation are very relevant parameters too.

In some studies, in which a high number of phages are used, the bacterial lysis ‘from without’ can occur because many viral particles bind to the bacterial surface, leading to the production of numerous holes in the cell wall [38,39]. All these concepts must be better studied and understood in order to apply phages to food pathogens.

Although the application of phages will continue, there is a phenomenon that must always be kept in mind, the emergence of phage-resistant strains. When infecting bacterial cells, phages already face a range of antiviral mechanisms (i.e., restriction modification systems/enzymes), and they have evolved multiple tactics to avoid these mechanisms. In this co-evolution between bacteria and phages, most authors agree that phages can effectively raise a counter-resistance. Therefore, finding a new phage that can infect a bacterium will always be easier than finding an entirely novel family of antibiotics.

We do not know much about how often these resistant variants of phages used in the food industry appear, as few publications include assays to study this phenomenon. It is likely that researchers prioritize the study of efficacy over safety. Moreover, multidrug resistance, where a bacterium has obtained resistance mechanisms against several different families of antibiotics, is increasingly common, but this phenomenon does not occur when phages are used. Additionally, many studies suggest that phage combinations can be optimized to limit the emergence and persistence of resistance, therefore promoting the long-term usefulness of phage therapy. With regards to this issue, enzybiotics offer the advantage that they do not generate resistance because they act on essential targets for the bacteria’s viability, so, it is difficult for bacteria to modify them.

The other most important issue in addition to the development of phage-resistant strains is phage spread. As bacteriophages applied to food can be easily transferred between facilities in the food industry, we must pay particular attention to the number of
phages used, and above all, to how they are applied to food. An undesirable effect would be the inactivation of starter cultures that initiate the fermentation processes. Despite the narrow spectrum of a specific phage, the problem of the phages spread within the food industries is real because it is not convenient; for example, to collaterally eliminate some species of lactic acid bacteria that confer characteristic properties to the products in which they are present [40].

As with isolated phages, phage cocktails can be used directly on food or surfaces and food handling tools in chain processing plants. Another advantage of phage cocktails is that they can be modified quickly and conveniently to deal with specific strains that may appear in a particular food manufacturing facility [41]. No articles were reviewed here where more than three bacteriophages or cocktails containing undefined strains were used because in the last few years there have been excellent reviews on that scope [26,41–43]. Moreover, Theuretzbacher’s recent article in the currently available weaponry against superbugs indicates that more than 20 different bacteriophage-based products have been approved for the control of pathogenic bacteria related to the food industries or direct food contamination [44].

Our review of approximately 100 bacteriophages indicates that three families (Myoviridae, Siphoviridae, and Podoviridae) account for the majority of virulent phages for the most common food-borne pathogen species. Much work has focused on the biocontrol or biopreservation of foods with six of the most important food-borne pathogens: E. coli (mainly serotype 015:H7), Listeria monocytogenes, Staphylococcus aureus, Clostridium spp., Campylobacter jejuni, and Salmonella spp., (Table 1). In addition to those six important food pathogens, phages against many other bacteria capable of causing foodborne infections should begin to be studied. This would allow us to identify not only new phages but also interesting enzybiotics.
Table 1. Phages tested against food-borne pathogens and their proposed use as food biopreservatives.

| Target Bacteria                      | Phage/s       | Source                  | Characterization Method | Genome Length | Family          | Food Application                                           | Reference |
|--------------------------------------|---------------|-------------------------|-------------------------|---------------|-----------------|-----------------------------------------------------------|-----------|
| *Aeromonas hydrophila*               | AH-1, AH-4, AH-5 | Sewage samples          | TEM                     | ND            | *Myoviridae*    | Depuration of artificially contaminated cockles           | [45]      |
| *Bacillus cereus*                    | PBC1          | Sewage sample           | TEM, sequencing         | 41,164 bp     | *Siphoviridae*  | Inhibition of *B. cereus* growth in boiled rice            | [46,47]   |
| *Brochothrix thermosphacta*          | A3            | Spoiled retail rib steaks | TEM                    | ND            | ND              | Control of bacterial strains during refrigerated storage  | [16,48]   |
| *Campylobacter jejuni*               | Cj6           | Unknown                 | -                       | ND            | ND              | Control of pathogens in liquid foods                      | [36,49]   |
| *C. jejuni*                          | 2             | Unknown                 | 1 dsDNA                | ~140 kb       | *Myoviridae*    | Reduction of *C. jejuni* contamination of retail poultry products | [50,51]   |
| *C. jejuni*                          | CP8, CP30     | Poultry excreta         | TEM, dsDNA             | ~140 kb       | *Myoviridae*    | Reduction of food-borne bacteria and biofilms             | [52,53]   |
| *C. jejuni*                          | 12673         | NCTC (UK)               | TEM, DNA sequencing     | ~135 kb       | *Myoviridae*    | Reduction of bacterial contamination on chicken carcass surfaces | [54,55]   |
| *Clostridium tyrobutyricum* and *C. sporogenes* | CTP1         | Landfill                | TEM, DNA sequencing     | 59,199 bp     | *Siphoviridae*  | Cheese manufacturing                                      | [56]      |
| *Cronobacter (Enterobacter)* sakazakii | ESP 1–3, ESP 732–1 | Sewage treatment plant | TEM, dsDNA             | ND            | *Siphoviridae*  | Control of *E. sakazakii* in reconstituted infant formula  | [57]      |
| *Escherichia coli*                   | PE37          | Bovine intestine samples | TEM, DNA sequencing     | 166,423 bp    | *Myoviridae*    | Biocontrol of *E. coli* STEC O157:H7 and ESBL EC           | [58]      |
| *E. coli*                            | EC6, EC9, EC11 | Sewage                  | TEM, dsDNA             | ND            | *Siphoviridae*  | Biocontrol against *E. coli* in UHT and raw bovine milk   | [59]      |
| *E. coli* (STEC) O145                | Ro145cIw      | Non-fecal compost samples | TEM, DNA sequencing     | 42,031 bp     | *Siphoviridae*  | Control of foodborne STEC O145                            | [60]      |
| *E. coli* O157:H7                    | vB_EcoS_FFH_1, vB_EcoS_FFH_1 | Wastewater treatment plants | TEM, sequencing       | 108,483 bp 139,020 bp | *Siphoviridae*  | Reduction of contamination in ground beef                | [61,62]   |
| *E. coli* O157:H7                    | eI1/2, eI4/1c, PP01 | Bovine farmyard samples | TEM, dsDNA             | ND            | ND              | Elimination or reduction of *E. coli* O157:H7 bacteria from meat carcasses | [63–65]   |
| *E. coli* O157:H7                    | FAHec1        | Raw screened sewage     | TEM, dsDNA             | ~90 kb        | *Myoviridae*    | Inactivation of *E. coli* O157:H7 on beef                 | [34,66]   |
### Table 1. Cont.

| Target Bacteria                              | Phage/s                          | Source                        | Characterization Method | Genome Length | 2 Family | Food Application                                                                 | Reference |
|----------------------------------------------|----------------------------------|-------------------------------|-------------------------|---------------|----------|----------------------------------------------------------------------------------|-----------|
| E. coli O157:H7                             | KH1, KH4, KH5                    | Cattle and sheep fecal samples | -                       | ND            | ND       | Elimination of O157:H7 from foods under refrigerated conditions. Reduction of E. coli on surfaces. | [67,68]   |
| E. coli O157:H7                             | ECML-4, ECML-117, ECML-134       | Fresh and salt water environments | TEM, DNA sequencing | 157,308 bp    | Myovirida | Reduction of contamination of hard surfaces and foods contaminated by E. coli O157:H7 | [69,70]   |
| E. coli strains, Salmonella and Shigella spp.| C203, P206                       | Cottage cheese and from poultry liver | TEM, DNA sequencing | 138,073 bp    | Myovirida | Biocontrol agent against E. coli EHEC O157                                       | [37]      |
| Shigatoxigenic E. coli Enteropathogenic E. coli | DT1, DT5, DT6                   | Stool samples of patients with diarrhea | TEM                    | ND            | Myovirida | Control of pathogenic E. coli in meat products and during milk fermentation       | [71,72]   |
| E. coli strains including serotype O157:H7   | OSY-SP                           | Manure from cattle, sheep, and horse farms | Pulsed-field gel electrophoresis (PFGE) | ~150 Kb       | Myovirida | Reduction of E. coli in fresh produce type (cut green pepper or spinach leaves) | [73]      |
| Lactobacillus brevis                        | SA-C12                           | Fresh silage                  | TEM                     | ND            | Myovirida | Control of L. brevis beer-spoilage                                                | [74]      |
| Leuconostoc gelidum                         | ggg                              | Vacuum-packaged pork          | TEM                     | ND            | Siphovirida | Inhibition of Leuconostoc in raw pork                                              | [75]      |
| Listeria monocytogenes                      | A500 ATCCΩ 23074-B1FM            | L. monocytogenes isolated from Guinea pig | TEM                    | 38,867 bp     | Siphovirida | Control of L-forms of L. monocytogenes on surfaces                               | [76,77]   |
| L. monocytogenes                            | H387, H387-A 2671                |                               | TEM                     | ND            | Siphovirida | Disinfection of working surfaces of food processing plants                         | [78,79]   |
| L. monocytogenes                            | LiMN4L, LiMN4p, LiMN17           | Seafood waste water treatment unit | ND                     | ND            | ND       | Control of L. monocytogenes on stainless steel in seafood processing environments | [22]      |
| L. monocytogenes                            | A511                             | Sewage from a sewage treatment plant | Phage typing, TEM, sequencing | 134,494 bp    | Myovirida | Ready-to-eat foods from plant and animal origin including cheeses                  | [80–84]   |
| L. monocytogenes                            | FWLLm1                           | Sheep feces                   | TEM,                    | ND            | ND       | Reduction of L. monocytogenes growth in ready-to-eat poultry products              | [85]      |
| L. monocytogenes                            | IZSAM-1                          | Floor drain-water from an Italian blue cheese dairy factory | TEM, sequencing         | ~50 kb        | Siphovirida | Biocontrol of L. monocytogenes within cheese industrial facilities               | [86,87]   |
| Target Bacteria                  | Phage/s       | Source                                      | Characterization Method | Genome Length | ² Family   | Food Application                                                                                   | Reference |
|---------------------------------|---------------|---------------------------------------------|-------------------------|---------------|------------|----------------------------------------------------------------------------------------------------|-----------|
| *Listeria* spp.                 | P100          | Sewage effluent from a dairy plant          | TEM, sequencing         | 131,384 bp    | *Myoviridae* | Biocontrol of contaminated surfaces, the surface of soft cheeses, ready-to-eat foods, fresh-cut fruit, and fruit juices, raw fish fillets, | [88–92]   |
| *Pseudomonas fragi*             | Wy            | Ground Beef                                 | TEM, dsDNA              | ND            | -          | Reduction of *P. fragi* in refrigerated raw milk                                               | [93–95]   |
| *Pseudomonas* sp.               | C35           | spoiled retail beef                         | -                       | ND            | -          | Biological control of beef spoilage                                                              | [96,97]   |
| *Pseudomonas lactis*            | HU1           | Sludge obtained after passing raw cow’s milk through a centrifugal clarifier | TEM, dsDNA             | ~48 Kb        | *Podoviridae* | Control of *P. lactis* in Raw Cow’s Milk                                                       | [98]      |
| *Pseudomonas fluorescens*       | PspYZU5415    | Sewage samples                              | TEM, sequencing         | 39,636 bp     | *Siphoviridae* Corticoviridae | Growth inhibition of *E. cloacae* and *P. fluorescens* in cucumber juice with different salt concentrations | [43]      |
|                                 | EcpYZU01      |                                            |                         | 39,767 bp     |            |                                                                                                    |           |
| *P. fluorescens*                | IBB-PF7A      | Sewage treatment plant                      | TEM, dsDNA              | ~42 kb        | *Podoviridae* | Biocontrol of *P. fluorescens* in dairy and other food industries                               | [99,100]  |
| *Salmonella Enteritidis*, *S. Typhimurium* | wkl3 | Chicken by-product samples                  | TEM, sequencing         | 42,766 bp     | *Siphoviridae* | Control *Salmonella* on chicken skin. from broiler carcasses                                    | [101]     |
| *Salmonella* serovars           | LPSEYT        | Water samples                               | TEM, sequencing         | 53,387 bp     | *Myoviridae* | Biocontrol of *Salmonella* in food matrices including milk and lettuce                           | [42]      |
| *Salmonella Enteritidis*        | CAU-SEP-1     | River water samples                         | TEM                     | ND            | *Myoviridae* and *Siphoviridae* | Control of *S. Enteritidis* in chicken breast meat                                               | [102]     |
|                                 | CAU-SEP-2     |                                            |                         |               |            |                                                                                                    |           |
|                                 | CAU-SEP-3     |                                            |                         |               |            |                                                                                                    |           |
|                                 | CAU-SEP-4     |                                            |                         |               |            |                                                                                                    |           |
| *Salmonella* Enteritidis        | CNPSA 1       | free-range chickens                         | TEM, dsDNA              | ND            | tailed dsDNA phages | Reduction of *Salmonella Enteritidis* in Contaminated Chicken Cuts                               | [103–105] |
|                                 | CNPSA3        |                                            |                         |               |            |                                                                                                    |           |
|                                 | CNPSA4        |                                            |                         |               |            |                                                                                                    |           |
| *Salmonella* Enteritidis        | P29C          | Raw human sewage                            | -                       | ND            | *Siphoviridae* | Reduction of bacterial contamination on chicken carcass surfaces                                 | [54,106]  |
| *Salmonella* spp.               | PSE5          | Poultry slaughterhouse wastewater           | plaque morphology and RAPD analysis | ND            | ND         | Reduction of contamination in raw chicken eggs                                                  | [107]     |
### Table 1. Cont.

| Target Bacteria | Phage/s | Source | Characterization Method | Genome Length | ² Family | Food Application | Reference |
|-----------------|---------|--------|-------------------------|---------------|----------|------------------|-----------|
| *Salmonella* spp. | LPSTLL, LPST94, LPST153 | Environmentally water samples | TEM | ND | Siphoviridae Ackermanniviridae Podoviridae | Reduction of *Salmonella* counts in milk and chicken breast on stainless still surfaces | [108,109] |
| *Salmonella* strains | LPSE1 | Environmental samples | TEM, dsDNA, sequencing | 41,854 bp | Siphoviridae | Control of *Salmonella* in ready-to-eat foods | [110] |
| *Salmonella* strains | Felix O1/Felix O1-E2 | Feces of paratyphoid B patients | TEM, Sequencing | 86,155 bp/~84 kb | Myoviridae | Suppression of *Salmonella* growth on chicken frankfurters, poultry products, and ready-to-eat foods | [111–114] |
| *Salmonella* strains | PHL4 | Wastewater treatment plant | - | ND | ND | Reduction of *Salmonella* growth poultry products | [115] |
| *Salmonella* strains | vB_SalS_SJ_3 | Wastewater | TEM, DNA sequencing | 162,910 bp | Siphoviridae | Biocontrol of *Salmonella* in contaminated Eggs and Pork | [116–118] |
| *Salmonella* strains | Pu20 | Sewage samples | TEM, sequencing | 59,435 bp | Podoviridae | Growth inhibition of *Salmonella* strains in liquid egg white and yolk | [119] |
| *Salmonella* strains | D1-2 | Environmental samples | TEM, sequencing | 86,878 bp | Myoviridae | Growth inhibition of *Salmonella* strains in liquid egg white and yolk | [120] |
| *Salmonella* Typhimurium | P22 [Argo4] | *Salmonella enterica* subsp. *enterica* serovar Typhimurium | TEM, sequencing, Reference strain ATCC® 97540™ | 41,724 bp | Podoviridae | Prevention of attachment to food surfaces and food matrices | [121–124] |
| *Salmonella* Typhimurium | P7 | Unknown | - | ND | ND | Control of pathogens in liquid foods | [36] |
| *Salmonella* serovars | LPST153 | Water samples | TEM, sequencing | 39,176 bp | *Autographivirinae* | Control of *Salmonella* in raw milk and raw beef sausages | [125] |
| *S. enterica* serovar Typhimurium | UAB_Phi20 | Chicken Chicken pig | TEM, dsDNA, sequencing | 41,809 bp 44,110 bp 87,669 bp | Podoviridae Podoviridae Myoviridae | Reduction of *Salmonella* on foods and reduction of *Salmonella* Colonization of poultry | [126–128] |
| *Salmonella* Enteritidis | SP-3 | Intestinal content of broiler chickens | TEM, dsDNA, PCR amplification | ~86 kb ~88 kb | Podoviridae *Siphoviridae* | Biocontrol of *Salmonella* in cooked chicken meat | [35,129,130] |
| *Salmonella* Enteritidis | SJ2 | Chicken egg | ND | ND | ND | Reduction of *Salmonella* counts in Cheddar cheese made from both raw and pasteurized milk, and in contaminated eggs and pork | [131] |
Table 1. Cont.

| Target Bacteria | Phage/s | Source | Characterization Method | Genome Length | 2 Family | Food Application | Reference |
|-----------------|---------|--------|-------------------------|---------------|----------|------------------|-----------|
| Salmonella Enteritidis | vBSenM-PA13076 (PA13076) vBSenM-PC2184 (PC2184) | Chicken sewage | TEM | 52,474 bp ND | Myoviridae | Biocontrol of Salmonella in foods (chicken breast, pasteurized whole milk, Chinese cabbage) | [132,133] |
| Salmonella and E. coli O157:H7 | PS5 | Raw chicken products | TEM, sequencing | 158,400 bp | Myoviridae | Reduction of viable counts on solid and liquid foods | [134] |
| Salmonella Oranienburg | SSP5 SSP6 | Sewage samples | TEM | ND | Myoviridae Siphoviridae | Control of Salmonella Oranienburg on alfalfa seeds | [135] |
| S. Typhimurium S. Enteritidis S. Montevideo | A B | sewage treatment plant | TEM | ND | Myoviridae Siphoviridae | Control of Salmonella in mustard and broccoli seeds | [136] |
| Salmonella strains, including MDR Salmonella | T156 | Waste water | TEM, dsDNA, sequencing | 123,849 bp | Siphoviridae | Microencapsulated bacteriophage applied in skim milk and lettuce for biocontrol of Salmonella | [137] |
| Staphylococcus aureus | ATCC® 19685-B1™ | Deposited by EA Asheshov | TEM | 139,831 bp | Myoviridae | Removing S. aureus biofilms | [138,139] |
| S. aureus | H5 (phiPLA88) A72 (phiPLA35) | Raw milk | TEM, dsDNA, sequencing | 42,526 bp 45,344 bp | Siphoviridae | Curd manufacturing, fresh and hard-type cheeses | [140–142] |
| S. aureus | SA46-CTH2 | Food samples | TEM | 17,505 bp | Podoviridae | Inactivation of S. aureus planktonic cells in pasteurized milk and biofilms on stainless steel surfaces | [143] |
| S. aureus | SA13m | Temperate phage SA13 isolated from a goat fecal sample | TEM, sequencing | 42,652 bp | Siphoviridae | Biocontrol of S. aureus in pasteurized whole milk at refrigeration and ambient temperatures | [144] |
| Shewanella baltica and S. putrefaciens | SppYZU01 to SppYZU10 | Wastewater from freshwater and marine product marketplaces | TEM, sequencing | SppYZU01 (43,567 bp) SppYZU05 (54,319 bp) | Myoviridae Siphoviridae | Biopreservation of chilled channel catfish | [145] |
| Shigella spp. | SF-A2 SD-11 SS-92 | Spiced chicken Pig farm effluent Pig farm effluent | TEM | ND | Myoviridae | inactivation of foodborne Shigella on ready-to-eat chicken | [146] |
| Vibrio parahaemolyticus | vB_VpaS_OMN (designated as phage OMN) | Sea water | TEM, sequencing | 42,202 bp | Podoviridae | Inactivation of V. parahaemolyticus in oyster meat | [147] |

1 Nuclease digestion tests and/or Random Amplified Polymorphic DNA Analyses (RAPD), 2 Family designated by the authors, ND: not determined, TEM: Transmission Electron Microscopy.
According to the articles analyzed, the phages of the family Myoviridae were preferentially used to control E. coli. Other important food pathogens such as C. jejuni, Salmonella, L. monocytogenes, and S. aureus were controlled by Siphoviridae and Myoviridae. The analyzed studies showed that the Podoviridae family can infect all these species, but fewer phage strains of this family have been found to control bacteria in the different foods tested. Comparative genomics and morphological observation by transmission electron microscopy revealed that the phage LPSEYT, able to infect Salmonella, represents a new genus within the Myoviridae family [42]. This last example shows that if we go a little deeper into the genomic characterization of the isolated strains, we will be able to advance in the knowledge of the taxonomy of phages. Most of the phages used to control these pathogen species in food were isolated from wastewater, sewage, or other environmental samples; but many have also been isolated from different foods. One phage strain (EcpYZU01) of the Corticoviridae family was isolated from sewage samples and tested against Enterobacter cloacae in cucumber juice [43]. Finally, a phage (LPST94) from the Ackermannviridae family isolated from water was effective against Salmonella in foods [108,109]. This newly assigned family was recently added to the list of the International Committee on Taxonomy of Viruses ICTV catalog. The isolation of phages from sewage and water samples is common due to their abundance in these ecosystems. However, Scattolini et al., pointed out that the search and characterization of phages isolated in the same foods in which the pathogens can hide could be a good way “to integrate this control measure in an innovative, cost-effective, safe and environmentally friendly way” [86]. Therefore, it seems like a good idea to use phages in food safety which in turn come from food, especially for the consumer, who can identify fewer drawbacks than when consuming phages or their genetically manipulated enzybiotics.

Bacteriophages can also be used to prevent or to reduce colonization of domesticated livestock with bacterial pathogens before they enter the production chain [148]. After that, phages can be used to decontaminate inanimate surfaces made, for example, of stainless steel or to fight bacterial biofilms. Finally, phages can be used directly on food, both in unprocessed or ready-to-eat foods as well as processed foods, even stored at temperatures ranging from 4 °C to 20 °C.

Several cofactors tested with phages used in the control of L. monocytogenes in the food industry have been recently reviewed by Kawacka and coworkers [26,149]. Among those factors, we can find other bacterial cultures such as Lactobacillus spp., Gluconobacter assii, the bacteriocins Nisin, Enterocin and Pediocin, and several compounds such as lauric arginate, potassium lactate, sodium diacetate, sucrose monolaurate.

3. Spatial Distribution of Phages

Bacteriophages’ ubiquity is another advantage. It is estimated that there are 10 bacteriophages for every bacterium present on our planet, representing a virtually unlimited source, not only of virions but also of lytic enzymes. Phages are especially abundant in seawater and soil and have also been found in large quantities in wastewater. The potential use of bacteriophages as indicators of environmental contamination has also been investigated in the last few decades [150–155]. Perhaps the most impressive figures are that phages kill bacteria at rates of up to 40% of the total population of marine bacteria per day and that carbon flux through phage biomass is estimated at 145 gigatonnes per year, playing a crucial role in our planet’s global carbon cycle [156,157]. They are also easily found on any animal or plant surfaces as they are part of the microbiota of most living things. Phages have also been isolated from a variety of foods, including ready-to-eat foods, fish and shellfish, milk products, meat, and vegetables [33,158–162]. Because of this, consumers are already in contact with food bacteriophages every day. Therefore, if researchers could offer an adequate explanation, it would help consumers to increase their acceptance of the use of food bacteriophages. In other words, they should accept their use as biopreservatives if we can explain well what this class of virus really is and how exactly they are used to fight “bad” bacteria in food.
4. Morphology and Classification

Initially, phages were characterized by transmission electron microscopy (TEM), followed by pulse-field gel electrophoresis and restriction endonuclease analysis. However, although TEM continues to be essential in publications on bacteriophage viruses, the quality of the images in many of the articles is questionable [163]. Most studies use the work of Ackermann or the criteria of the International Committee on Taxonomy of Viruses (ICTV) [164] to identify their phage isolates [165–167]. For further taxonomic classification and phage characterization, more detailed information, such as genomic data, has begun to be included in scientific publications [168–171].

Most phages belong to the order Caudovirales. Based on the tail morphology, Caudovirales are divided into three families: Myoviridae, Siphoviridae, and Podoviridae. Myoviridae phages are characterized by long straight contractile tails, Siphoviridae phages possess long flexible non-contractile tails, and Podoviridae phages have short, non-contractile tails [172].

Alternatively, we can also use the PCR technique and subsequent sequencing to partially characterize the isolated phages. For example, some authors used specific primers to detect the Major Capsid Protein (MCP) of reported Salmonella phages [158,159].

Augustine et al., also used PCR or multiplex PCR to perform a screening of virulence factors in DNA obtained from phages [35]. Tomat et al. used PCR to detect virulence factor genes (from diarrheagenic E. coli toxins) in two phages (DT1 and DT6) isolated from stool samples of patients with diarrhea [72].

Presently, full genome sequencing and analysis provide the key tool for taxonomic classification and for alerting the presence of “dangerous” genes that phage genomes may contain. We believe that it is necessary to sequence phage genomes to obtain information on the presence of antibiotic-resistant genes or virulence factors before determining their suitability for food applications. An outline with the steps followed for the isolation and characterization of phages for food biopreservation is shown in Figure 1.

![Figure 1. Steps followed for the isolation and characterization of phages.](image-url)

DNA genomes of Caudovirales range in size from about 15 up to 500 kbp [173]. The study of the genome of phages is crucial today, but most investigations analyzed before to the last 10 years do not include the sequencing or annotation of these genomes. The complete genomes of phages are already included as a technique of characterization and phylogeny, but the in-depth analysis of these genomes has only been carried out very recently; this even allows us to discover new subfamilies and new genera of phages infecting food pathogens [43,125].
5. Phage’s Life Cycle

To perpetuate themselves, phages must infect their host bacteria by binding to specific receptors on them. After injecting their nucleic acid into the bacterium’s cytoplasm, phages can hijack the bacterium’s cellular machinery to induce their own replication, through a process called the “lytic cycle”, giving rise to hundreds or thousands of complete viral particles that will leave the cell after killing it (Figure 2). Alternatively, if the phage nucleic acid is inserted into the chromosome or within a plasmid of the bacterium, it can remain in a kind of dormant state known as the “lysogenic cycle,” which will not produce new virus particles until conditions are favorable, or their genes are activated by some external stimulus. Lytic bacteriophages are the first choice to selectively kill bacteria in foods because lysogenic phages remain in the bacterial chromosome and will not multiply until the environment in which the bacterium is found allows for it, making lysogenic phages difficult to control.

Figure 2. Gram-negative bacterium after lysis by phages. Numerous complete or incomplete phage heads and tails can be seen in the image. Inset: Detail of the boxed area showing two phages of the Siphoviridae family. Original magnification ×25,000.

6. Enzybiotics

There are three classes of bacterial cell wall hydrolases: animal lysozymes, bacterial autolysins, and phage lysins. All animal lysozymes share the ability to hydrolyze the β-(1,4)-glycosidic bond between the alternating N-acetylmuramic acid and N-acetylglucosamine residues of the bacterial cell wall polymer called peptidoglycan. Their biological role is mainly antibacterial defense, but some lysozymes also work as food digestive enzymes in animal guts [174]. Bacterial cell wall hydrolases are involved in carefully remodeling the cell wall to maintain cell integrity but also participate actively in processes such as cell division, bacterial surface appendages’ assembly, and the facilitation of bacterial secretion systems’ stabilization [175,176]. Most of these autolysins are peptidoglycan hydrolases (PGHs) that can provoke bacterial autolysis, so their expression and activity need to be tightly regulated.

The third class of cell wall hydrolases are phage endolysins, enzymes that directly target bonds in the peptidoglycan of the bacterial cell wall. These so-called enzybiotics
Molecules 2021, 26, 5138

(Edited) (for ENZYme antiBIOTICS) are synthesized at the end of the bacteriophage lytic cycle to lyse the bacterium they parasitize, producing a lysis “from within” in Gram-negative bacteria [177]. Most endolysins contain one or two enzymatically active domains (EAD) in the N-terminus (which cleave one of the bonds in the bacterial peptidoglycan) and one cell wall-binding domain (CBD) in the C-terminal region (which is involved in host bacterial recognition). Based on their EAD, enzybiotics can be broadly divided into three types: endopeptidases, amidases, and glycosidases.

On the other hand, in Gram-positive bacteria, endolysins are also able to lyse bacteria “from outside” during the phage adsorption at the bacterial surface [178,179].

Endolysins have an extensive structural variation and a diverse cleavage predilection for the molecules with glycosidic, amide, or peptide bonds present in the bacterial peptidoglycan [180,181]. The structure of endolysins can be either globular or modular. Globular endolysins are unique for phages infecting Gram-negative bacteria, whereas modular endolysins are found in phages with a Gram-positive host. Another class of phage enzymes is virion-associated peptidoglycan hydrolases which share a similar mode of action on the bacterial peptidoglycan [182–185]. A good example of these newly studied antibacterial molecules is the virion-associated peptidoglycan hydrolase HydH5 of Staphylococcus aureus bacteriophage vB_SauS-phiPLA88 [186]. Additionally, some phages can produce depolymerases to overcome bacterial protective layers such as proteinaceous S-layers [187] or polysaccharide capsules [188].

Among the advantages of enzybiotics, we include the possibility of totally or partially breaking the structure of bacterial biofilms. A biofilm can be defined as a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. Growth in biofilms enhances the survival of bacterial populations in the food industry environments, increasing the probability of causing food-borne infections. Due to the presence of extracellular material that protects biofilms, many phages have limited access to bacteria inside these structures. This can be solved using phages expressing exopolysaccharide depolymerases and endolysins. Endolysins can act effectively irrespective of the metabolic status of the cells (exponential and stationary phase cells) and are capable of killing planktonic cells as well as sessile cells. In this way, phage endolysins have been shown to be effective in eliminating biofilms formed by tenacious pathogens on different surfaces commonly used in the food industry [189–192]. Moreover, endolysins can be evaluated in combination with depolymerases or even with antibiotics to kill the underlying pathogen that formed the biofilm. On the other hand, as many pathogens build their biofilms based on different substances that form the biofilm matrix, it would be advisable to evaluate the activity of endolysins against biofilms that present a different proportion of proteins, nucleic acids, sugars or lipids.

Additionally, endolysins can kill “persister” bacteria that escape conventional antibiotics and even can kill the dreaded multi-resistant strains. Although there are not many studies in this regard, endolysins also offer the possibility of being used in combination with other molecules or with other solutions for the food industry, such as bacteriocins or probiotics. Furthermore, as gene-encoded proteins, enzybiotics are amenable to bioengineering strategies, both to optimize specificity and to increase yields [193,194]. An example is the construction of hybrid proteins consisting of LysSA11—an endolysin of the S. aureus phage SA11 and the enzymatically active domain of LysB4—and endolysin from the Bacillus cereus phage B4 [195].

The search, characterization, and practical use of these phage-derived lysins have received less attention than phages, basically because they are more difficult for many laboratories to study. However, there is a growing body of work on these enzymes, particularly in the field of human and animal pathogens, which has encouraged researchers in other fields, including food safety, to begin promising work with enzybiotics. Not surprisingly, many enzybiotics have been successfully tested as biopreservatives or have been proposed by their discoverers as good candidates to be used in food against Gram-negative and Gram-positive bacteria (Table 2). The study of these enzymes in phages that
do not belong to the “selective group” of food pathogens could provide a wide range of new proteins with different properties and varied spectra.

**Table 2.** Enzybiotics tested against food-borne pathogens and their proposed use in foods.

| Target Bacteria | Enzybiotic | Source | Food Application | Reference |
|-----------------|------------|--------|------------------|-----------|
| *Bacillus cereus*, *B. subtilis* and *L. monocytogenes* | LysB4 | *B. cereus* phage B4 | antibacterial agent to control foodborne pathogens. | [196] |
| *Clostridium tyrobutyricum* and *C. sporogenes* | Ctp1L | Bacteriophage CTP1 isolated from landfill | Cheese manufacture; reduction of clostridial activity in cheese | [56,197] |
| *C. tyrobutyricum* and *C. acetobutylicum* | CS74L | Lytic bacteriophage (ATCC® 8074-B1™) of *C. sporogenes* | Biocontrol of clostridia strains in foods | [198] |
| *C. perfringens* | Ply3626 | *C. perfringens* ATCC 3626 | Control of anaerobic spore-formers | [199] |
| *C. perfringens* | LysCPAS15 | *C. perfringens* phage CPAS-15 | Inhibition of *C. perfringens* in sterilized milk | [200] |
| *Bacillus subtilis* and *B. megaterium* and *L. monocytogenes* | PLY118, PLY500 PLY 511 | Phages from *Listeria monocytogenes* | Production of airy starter cultures with biopreservation properties | [201–203] |
| *E. coli O157:H7* | PlyEc2 | Phage from *E. coli* | Reduction of *E. coli O157:H7* on contaminated lettuce | [204] |
| *Lactobacillus lactis*, *Pediococcus acidilactici* and *P. pentosaceus* | LysA2 | *L. casei* bacteriophage A2 | Ripening of fermented products | [205] |
| *Lactobacillus*, *lactococci*, *pediococci*, *B. Subtilis* | Mur-LH | Phage 0303 from *Lactobacillus helveticus* CNRZ 303 | Preventing the growth of spoilage microbes | [17] |
| *L. monocytogenes* and *B. subtilis* | PlyPi00 | Phage from *L. monocytogenes* | Antimicrobial biopreservative in fresh cheese. | [206] |
| *L. monocytogenes* | LysZ5 | Phage from *L. monocytogenes* | Control pathogens in soya milk | [207] |
| *L. monocytogenes* | PlyLM | Phage from *L. monocytogenes* strain 4b | Proposed control of *L. monocytogenes* in food matrices and processing facilities | [208] |
| *L. monocytogenes* | HPL118 HPLS00 HPLS11 HPLP35 | Recombinant endolysins from *L. monocytogenes* phages | Reduction of *L. monocytogenes* viable counts in iceberg lettuce. Promising perspectives in production and packaging environments | [201,209,210] |
| Methicillin-resistant *S. aureus* | LysGH15 | Phage isolated from Sewage samples | Biopreservative in whole and skim milk | [211,212] |
| Methicillin-resistant *S. aureus* | LysSA11 | *Staphylococcus aureus* phage SA11 | Biocontrol of *S. aureus* on strain in pasteurized milk or ham and utensils | [213] |
| *S. aureus* Bacillus cereus | Hybrid LysB4EAD-LysSA11 | Phage SA11 from *S. aureus* phage B4 S from *B. cereus* | Biocontrol of *S. aureus* and *B. cereus* in boiled rice | [195] |
| *S. aureus* | LysH5 | Staphylococcal bacteriophage phi-SauS-IPLA88 | Disinfection process of industrial food facilities. Elimination of *S. aureus* in pasteurized milk | [190,214] |
| *S. aureus* | CHAPSH3b | Chimeric protein (CHAP domain from peptidoglycan hydrolase HydH5 and the SH3b cell wall-binding domain from lysostaphin) | *S. aureus* biofilm elimination | [215] |
| *S. aureus* | CHAPk | Truncated derivative of the phage lysin LysK from the staphylococcal bacteriophage K | Reduction of biofilm formation in processing systems | [189] |
| *S. aureus* | HydH5 HydH5Lyso HydH5SH3b CHAPSH3b and lysostaphin | *S. aureus* bacteriophage vB_SauS-philPLA88 | Biocontrol of *S. aureus* in dairy products | [216] |
| *Streptococcus spp.* | ASA2 | *Streptococcus agalactiae* (serotype III GBS strain 3330) bacteriophage B30 | Inactivation of *Streptococcus* spp. in cow milk | [217,218] |
| *S. Typhimurium* | LysSTG2 | *Salmonella*-lytic bacteriophage STG2 | Combating *S. Typhimurium* biofilms in food industries | [219] |
| *Salmonella strains* | LysSE24 | *Salmonella* phage LPSE1 | Food Control of *Salmonella* strains | [220] |
| Several Gram-negative pathogens, particularly against *Salmonella Typhimurium* | Lys68 | *Salmonella* phage phi68 isolated from feces from a poultry farm | Combat Gram-negative pathogens in the food industry | [221] |
Furthermore, enzybiotics can improve the narrow host spectrum of phages against both Gram-positive and Gram-negative bacteria. Therefore, the narrow host range of phages should be used to control specific spoilage or pathogenic bacteria, while the broadest spectrum of enzybiotics can be used to control different strains or species. Some of the newly isolated and characterized endolysins have a broad spectrum so they could be candidates for use in the food industry. An example is endolysin M4Lys, which has a peculiar mosaic structure [222].

The main limitation in the use of phage enzybiotics in food is their complicated production and purification, since relatively large amounts of proteins are needed even to be studied in in vitro assays. Another problem is their low resistance to high temperatures used in different processes in the food industry, such as disinfection. However, the search for new enzymes with new properties will make it possible to find thermostable and easy-to-produce forms in heterologous hosts such as *E. coli* and *Lactococcus lactis* [21,221,223–225].

7. Concluding Remarks

Many natural and eco-friendly methodologies for food preservation have been proposed in the last few years, but only limited data are available about the usefulness of most of them under industrial scale conditions, which needs proper attention to satisfy the requirements of the industry as well as the demand of the consumers [226–230]. Consequently, studies about the ability of the reported biopreservative agents to control the development of undesirable microorganisms when applied at the industrial scale are greatly required.

Studies on the biocontrol of food-borne pathogens in foods have generally produced very good results. However, not all are lights in the use of phages against pathogenic bacteria in food, there are also shadows. There are assays in which it was not possible to reduce the number of pathogenic bacteria in food using bacteriophages [136,231,232].

The use of phages in human and veterinary medicine has received much more attention than their use in the food industry; but the increasing appearance of antibiotic-resistant strains in the food industry has begun to make these viruses be seriously taken into account when seeking their (application for food safety), also in this context. Similarly, their lytic enzymes have not been sufficiently exploited in the food industry to date. However, this is beginning to change; indeed, after the successful use of lysozyme (animal) or Nisin (bacteria), enzymes are beginning to be seriously valued in the food industry. Phages offer new and interesting possibilities when planning the control of annoying microorganisms in food manufacturing, food biopreservation, or food processing. Additionally, their lytic enzymes, easily modifiable through molecular biology processes, offer a very wide range of possibilities both for direct application against bacteria, as well as for inclusion in food matrices or the preparation of antibacterial surfaces generated by biotechnology [233].

Virulent bacteriophages are naturally present in foods, therefore both phages and their enzybiotics would be exploited in different ways for food safety as the consumer demand for the use of ecofriendly biopreservatives is increasing. Contamination of ready-to-eat products with pathogenic bacteria is a more serious problem than the contamination of food that will then be cooked before being consumed since many of the cooking methods reduce the number of these bacteria. In this context, both phage and enzybiotics have been tested in ready-to-eat meals. However, not only is the use of phages and their enzymes in food is not only an area of incipient research, but the whole biology of phages is experiencing a new boom in all domains of research, mainly in human and veterinary health, where spectacular achievements have already been reached in some patients and farm animals.

Along with this increasing amount of isolation and characterization of phage strains capable of controlling important food-borne pathogens—it is always desirable to increase our armament against superbugs—we must make a parallel effort to understand more in-depth their interaction with target pathogens, as well as their biology and ecology in food if we want to apply them in the different stages of the production chain, increasing their biopreservation capacity. At the molecular level, we must better characterize enzybiotics,
study the possibility of applying them in different processes, and optimize their production so that their application is profitable for food producers and does not raise the price too much for consumers.

Furthermore, the safety and ubiquity of phages must be well explained to both food producers and consumers to avoid rejection of “the unknown” [234,235]. Bacteriophages are the most abundant microorganisms on the planet and even in our guts, with approximately 10^{14} phage particles in our body [236]. As we have seen in this review, phages and their enzybiotics can be found in the environment, in animals, and in food we eat every day. Finally, some phage-based products for the control of pathogens in food are already being used in different countries after being approved by competent authorities, even in ready-to-eat products. Those products mainly include a cocktail of phages, for example against E. coli (EcoShield™), L. monocytogenes (ListShield™ and PhageGuard Listex™), and Salmonella spp. (SALmoFresh™) [237].

**Author Contributions:** Conceptualization, J.R.-V.; writing—original draft preparation, J.R.-V., M.E.-Z., M.L.S.; writing—review and editing, J.R.-V., M.E.-Z., M.L.S., A.P.B.; Visualization: T.Y.F.-H.; supervision F.G., M.B. All authors have read and agreed to the published version of the manuscript.

**Funding:** Research in our group was supported by SODERCAN (Project RH20-XX-032, FAGOFOD).

**Acknowledgments:** Tamara Y. Forbes-Hernández is supported by a “Juan de la Cierva-Formación” post-doctoral contract.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study, or in the writing of the manuscript.

**References**

1. Lundén, J.; Björkroth, J.; Korkeala, H. Contamination Routes and Analysis in Food Processing Environments. In *Handbook of Hygiene Control in the Food Industry*; Lelied, H.L.M., Holah, M.A., Eds.; Woodhead Publishing Series in Food Science, Technology and Nutrition; Woodhead Publishing: Cambridge, UK, 2005; pp. 539–555.

2. Alegbeleye, O.O.; Singleton, I.; Sant’Ana, A.S. Sources and Contamination Routes of Microbial Pathogens to Fresh Produce during Field Cultivation: A Review. *Food Microbiol.* 2018, 73, 177–208. [CrossRef]

3. Olaimat, A.N.; Holley, R.A. Factors Influencing the Microbial Safety of Fresh Produce: A Review. *Food Microbiol.* 2012, 32, 1–19. [CrossRef]

4. Kim, N.H.; Cho, T.J.; Rhee, M.S. Current Interventions for Controlling Pathogenic *Escherichia coli*. *Adv. Appl. Microbiol.* 2017, 100, 1–47. [CrossRef] [PubMed]

5. Rajan, K.; Shi, Z.; Ricke, S.C. Current Aspects of *Salmonella* Contamination in the US Poultry Production Chain and the Potential Application of Risk Strategies in Understanding Emerging Hazards. *Crit. Rev. Microbiol.* 2017, 43, 370–392. [CrossRef] [PubMed]

6. Laroute, V.; Tormo, H.; Couderc, C.; Mercier-Bonin, M.; Le Bourgeois, P.; Cocaign-Bousquet, M.; Daveran-Mingot, M.-L. From Genome to Phenotype: An Integrative Approach to Evaluate the Biodiversity of *Lactococcus Lactis*. *Microorganisms* 2017, 5, 27. [CrossRef] [PubMed]

7. Klaenhammer, T.R. Genetics of Bacteriocins Produced by Lactic Acid Bacteria. *FEMS Microbiol. Rev.* 1993, 12, 39–85. [CrossRef]

8. Kang, M.-S.; Lee, D.-S.; Lee, S.-A.; Kim, M.-S.; Nam, S.-H. Effects of Probiotic Bacterium *Weissella cibaria* CMU on Periodontal Health and Microbiota: A Randomised, Double-Blind, Placebo-Controlled Trial. *BMC Oral Health* 2020, 20, 243. [CrossRef] [PubMed]

9. Jeong, J.H.; Lee, C.Y.; Chung, J.K. Probiotic Lactic Acid Bacteria and Skin Health. *Crit. Rev. Food Sci. Nutr.* 2016, 56, 2331–2337. [CrossRef] [PubMed]

10. Esber, N.; Mauras, A.; Delannoy, J.; Labelle, C.; Mayeure, C.; Caillaud, M.-A.; Kashima, T.; Souchaud, L.; Nicolis, I.; Kapel, N.; et al. Three Candidate Probiotic Strains Impact Gut Microbiota and Induce Anergy in Mice with Cow’s Milk Allergy. *Appl. Environ. Microbiol.* 2020, 86, e01203-20. [CrossRef] [PubMed]

11. Paparo, L.; Nocerino, R.; Di Scala, C.; Della Gatta, G.; Di Costanzo, M.; Buono, A.; Bruno, C.; Berni Canani, R. Targeting Food Allergy with Probiotics. *Adv. Exp. Med. Biol.* 2019, 1125, 57–68. [CrossRef]

12. de Sapieka, M.E.; Sgardioli, B.; Cámera, S.P.A.; Poeta, P.; Malcata, F.X. Current Trends of Enterococci in Dairy Products: A Comprehensive Review of Their Multiple Roles. *Foods 2021*, 10, 821. [CrossRef]

13. De Silva, L.A.D.S.; Wickramanayake, M.V.K.S.; Hoo, G.-J. Virulence and Antimicrobial Resistance Potential of *Aeromonas* Spp. Associated with Shellfish. *Lett. Appl. Microbiol.* 2021, 73, 176–186. [CrossRef]

14. Luque-Sastre, L.; Arroyo, C.; Fox, E.M.; McMahon, B.J.; Bai, L.; Li, F.; Fanning, S. Antimicrobial Resistance in *Listeria* Species. *Microbiol. Spectr.* 2018, 6. [CrossRef]
Molecules 2021, 26, 5138

15. Goodridge, L.; Abedon, S.T. Bacteriophage Biocontrol and Bioprocessing: Application of Phage Therapy to Industry. *Soc. Ind. Microbiol. News* 2003, 53, 254–262.

16. Greer, G.G. Bacteriophage Control of Foodborne Bacteri. *J. Food Prot.* 2005, 68, 1102–1111. [CrossRef] [PubMed]

17. Deutsch, S.-M.; Guezenec, S.; Piot, M.; Foster, S.; Lortal, S. Mur-LH, the Broad-Spectrum Endolysin of *Lactobacillus helveticus* Temperate Bacteriophage Phi-0030. *Appl. Environ. Microbiol.* 2004, 70, 96–103. [CrossRef]

18. Röhrig, C.; Huemer, M.; Lorg, D.; Luterbacher, S.; Pothenform, P.; Schefer, C.; Sobieraj, A.M.; Zinsli, L.V.; Maipady Shambat, S.; Leimer, N.; et al. Targeting Hidden Pathogens: Cell-Penetrating Enzymiotics Eradicate Intracellular Drug-Resistant *Staphylococcus aureus*. *mBio* 2020, 11, e00209-20. [CrossRef]

19. Dams, D.; Briers, Y. Enzybiotics: Enzyme-Based Antibacterials as Therapeutics. *Adv. Exp. Med. Biol.* 2019, 1148, 233–253. [CrossRef]

20. Gerstmans, H.; Rodriguez-Rubio, L.; Lavigne, R.; Briers, Y. From Endolysins to Artilysins®: Novel Enzyme-Based Approaches to Kill Drug-Resistant Bacteria. *Biochem. Soc. Trans.* 2016, 44, 123–128. [CrossRef]

21. Gutiérrez, D.; Rodriguez-Rubio, L.; Martinez, B.; Rodriguez, A.; Garcia, P. Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry. *Front. Microbiol.* 2016, 7, 825. [CrossRef]

22. Ganegama Arachchi, G.J.; Cridge, A.G.; Dias-Wanigasekera, B.M.; Cruz, C.D.; McIntyre, L.; Liu, R.; Flint, S.H.; Mutukumira, A.N. Effectiveness of Phages in the Decontamination of *Listeria monocytogenes* Adhered to Clean Stainless Steel, Stainless Steel Coated with Fish Protein, and as a Biofilm. *J. Ind. Microbiol. Biotechnol.* 2013, 40, 1105–1116. [CrossRef]

23. Soni, K.A.; Nannapaneni, R. Removal of *Listeria monocytogenes* Biofilms with Bacteriophage P100. *J. Food Prot.* 2010, 73, 1519–1524. [CrossRef]

24. Sillankorva, S.; Neubauer, P.; Azeredo, J. Phage Control of Dual Species Biofilms of *Pseudomonas fluorescens* and *Staphylococcus lentus*. *Biofouling* 2010, 26, 567–575. [CrossRef]

25. Ghosh, C.; Sarkar, P.; Issa, R.; Haldar, J. Alternatives to Conventional Antibiotics in the Era of Antimicrobial Resistance. *Trends Microbiol.* 2019, 27, 323–338. [CrossRef]

26. Kawacka, I.; Olejnik-Schmidt, A.; Schmidt, M.; Sip, A. Effectiveness of Phage-Based Inhibition of *Listeria monocytogenes* in Food Products and Food Processing Environments. *Microorganisms* 2020, 8, 1764. [CrossRef]

27. Zaburlin, D.; Quiberoni, A.; Mercanti, D. Changes in Environmental Conditions Modify Infection Kinetics of Dairy Phages. *Food Environ. Virol.* 2017, 9, 270–276. [CrossRef] [PubMed]

28. Payne, R.J.; Phil, D.; Jansen, V.A. Phage Therapy: The Peculiar Kinetics of Self-Replicating Pharmaceuticals. *Clin. Pharmacol. Ther.* 2000, 68, 225–230. [CrossRef] [PubMed]

29. Shao, Y.; Wang, L.-N. Bacteriophage Adsorption Rate and Optimal Lysis Time. *Genetics 2008*, 180, 471–482. [CrossRef] [PubMed]

30. Gaspár, S.; Rontó, G.; Müller, G. Determination of the Biological Parameters of Bacterium-Phage Complexes. *Z. Allg. Mikrobiol.* 1979, 19, 163–169. [CrossRef] [PubMed]

31. Abedon, S.T. Kinetics of Phage-Mediated Biocontrol of Bacteria. *Foodborne Pathog. Dis.* 2009, 6, 807–815. [CrossRef]

32. Sillankorva, S.; Neubauer, P.; Azeredo, J. Phage Control of Dual Species Biofilms of *Pseudomonas fluorescens* and *Staphylococcus lentus*. *Biofouling* 2010, 26, 567–575. [CrossRef]

33. Goodridge, L.; Abedon, S.T. Bacteriophage Biocontrol and Bioprocessing: Application of Phage Therapy to Industry. *Soc. Ind. Microbiol. News* 2003, 53, 254–262.

34. Augustine, J.; Louis, L.; Varghese, S.M.; Bhat, S.G.; Kishore, A. Isolation and Partial Characterization of *Escherichia coli* O157:H7 on Cooked and Raw Beef. *Food Sci. Technol. Int.* 2015, 21, 104–109. [CrossRef] [PubMed]

35. Hudson, J.A.; Billington, C.; Carey-Smith, G.; Greening, G. Bacteriophages as Biocontrol Agents in Food. *J. Food Prot.* 2005, 68, 426–437. [CrossRef]

36. Hudson, J.A.; Billington, C.; Wilson, T.; On, S.L.W. Effect of Phage and Host Concentration on the Inactivation of *Escherichia coli* O157:H7 on Cooked and Raw Beef. *Food Sci. Technol. Int.* 2015, 21, 104–109. [CrossRef] [PubMed]

37. Lutterbacher, S.; Pothenform, P.; Schefer, C.; Sobieraj, A.M.; Zinsli, L.V.; Maipady Shambat, S.; Leimer, N.; et al. Targeting Hidden Pathogens: Cell-Penetrating Enzymiotics Eradicate Intracellular Drug-Resistant *Staphylococcus aureus*. *mBio* 2020, 11, e00209-20. [CrossRef]

38. Duarte, J.; Pereira, C.; Costa, P.; Almeida, A. Bacteriophages with Potential to Inactivate *Aeromonas hydrophila* in Cockles: In Vitro and In Vivo Preliminary Studies. *Antibiotics* 2021, 10, 710. [CrossRef] [PubMed]

39. Röhrig, C.; Huemer, M.; Lorg, D.; Luterbacher, S.; Pothenform, P.; Schefer, C.; Sobieraj, A.M.; Zinsli, L.V.; Maipady Shambat, S.; Leimer, N.; et al. Targeting Hidden Pathogens: Cell-Penetrating Enzymiotics Eradicate Intracellular Drug-Resistant *Staphylococcus aureus*. *mBio* 2020, 11, e00209-20. [CrossRef] [PubMed]
46. Kong, M.; Kim, M.; Ryu, S. Complete Genome Sequence of Bacillus cereus Bacteriophage PBC1. J. Virol. 2012, 86, 6379–6380. [CrossRef] [PubMed]

47. Kong, M.; Ryu, S. Bacteriophage PBC1 and Its Endolysin as an Antimicrobial Agent against Bacillus cereus. Appl. Environ. Microbiol. 2015, 81, 2274–2283. [CrossRef]

48. Greer, G.G. Psychrotrophic Brothrix thermosphacta Bacteriophages Isolated from Beef. Appl. Environ. Microbiol. 1983, 46, 245–251. [CrossRef] [PubMed]

49. Carey-Smith, G.V. The Use of Bacteriophages as a Biocontrol Mechanism for Campylobacter and Salmonella Contaminants of Food. Master’s Thesis, School of Biological Sciences, University of Canterbury, Christchurch, New Zealand, 2004.

50. Atterbury, R.J.; Connerton, P.L.; Dodd, C.E.R.; Rees, C.E.D.; Connerton, I.F. Application of Host-Specific Bacteriophages to the Surface of Chicken Skin Leads to a Reduction in Recovery of Campylobacter jejuni. Appl. Environ. Microbiol. 2003, 69, 6302–6306. [CrossRef] [PubMed]

51. Sails, A.D.; Wareing, D.R.; Bolton, F.J.; Fox, A.J.; Curry, A. Characterisation of 16 Campylobacter jejuni and C. coli Typing Bacteriophages. J. Med. Microbiol. 1998, 47, 123–128. [CrossRef]

52. Siringan, P.; Connerton, P.L.; Payne, R.H.; Connerton, I.F. Bacteriophage-Mediated Dispersal of Campylobacter jejuni Biofilms. Appl. Environ. Microbiol. 2011, 77, 3320–3326. [CrossRef]

53. Loc Carrillo, C.; Atterbury, R.J.; el-Shibiny, A.; Connerton, P.L.; Dillon, E.; Scott, A.; Connerton, I.F. Bacteriophage Therapy to Reduce Campylobacter jejuni Colonization of Broiler Chickens. Appl. Environ. Microbiol. 2005, 71, 6554–6563. [CrossRef] [PubMed]

54. Goode, D.; Allen, V.M.; Barrow, P.A. Reduction of Experimental Salmonella and Campylobacter Contamination of Chicken Skin by Application of Lytic Bacteriophages. Appl. Environ. Microbiol. 2003, 69, 5032–5036. [CrossRef]

55. Kropinski, A.M.; Arutyunov, D.; Foss, M.; Cunningham, A.; Ding, W.; Singh, A.; Pavlov, A.R.; Henry, M.; Evoy, S.; Kelly, J.; et al. Genome and Proteome of Campylobacter jejuni Bacteriophage NCTC 12673. Appl. Environ. Microbiol. 2011, 77, 8265–8271. [CrossRef]

56. Mayer, M.J.; Payne, J.; Gasson, M.J.; Narbad, A. Genomic Sequence and Characterization of the Virulent Bacteriophage PhiCTP1 from Clostridium tyrobutyricum and Heterologous Expression of Its Endolysin. Appl. Environ. Microbiol. 2010, 76, 5415–5422. [CrossRef]

57. Kim, K.-P.; Klumpp, J.; Loessner, M.J. Enterobacter sakazakii Bacteriophages Can Prevent Bacterial Growth in Reconstituted Infant Formula. Int. J. Food Microbiol. 2007, 115, 195–203. [CrossRef]

58. Son, H.M.; Duc, H.M.; Masuda, Y.; Honjo, K.-I.; Miyamoto, T. Application of Bacteriophages in Simultaneously Controlling Escherichia coli O157:H7 and Extended-Spectrum Beta-Lactamase Producing Escherichia coli. Appl. Microbiol. Biotechnol. 2018, 102, 10259–10271. [CrossRef] [PubMed]

59. McLean, S.K.; Dunn, L.A.; Palombo, E.A. Phage Inhibition of Escherichia coli in Ultrahigh-Temperature-Treated and Raw Milk. Foodborne Pathog. Dis. 2013, 10, 956–962. [CrossRef]

60. Liao, Y.-T.; Salvador, A.; Harden, L.A.; Liu, F.; Lavenburg, V.M.; Li, R.W.; Wu, V.C.H. Characterization of a Lytic Bacteriophage as an Antimicrobial Agent for Biocontrol of Shiga Toxin-Producing Escherichia coli O145 Strains. Antibiotics 2019, 8, 74. [CrossRef] [PubMed]

61. Hong, Y.; Pan, Y.; Ebner, P.D. Meat Science and Muscle Biology Symposium: Development of Bacteriophage Treatments to Reduce Escherichia coli O157:H7 Contamination of Beef Products and Produce. J. Anim. Sci. 2014, 92, 1366–1377. [CrossRef]

62. Hong, Y.; Pan, Y.; Harman, N.J.; Ebner, P.D. Complete Genome Sequences of Two Escherichia coli O157:H7 Phages Effective in Limiting Contamination of Food Products. Genome Announc. 2014, 2, e00519-14. [CrossRef]

63. O’Flynn, G.; Ross, R.P.; Fitzgerald, G.P.; Coffey, A. Evaluation of a Cocktail of Three Bacteriophages for Biocontrol of Escherichia coli O157:H7. Appl. Environ. Microbiol. 2004, 70, 3417–3424. [CrossRef]

64. Akusobi, C.; Chan, B.K.; Williams, E.S.C.P.; Wertz, J.E.; Turner, P.E. Parallel Evolution of Host-Attachment Proteins in Phage PP01 Populations Adapting to Escherichia coli O157:H7. Pharmaceuticals 2018, 11, 60. [CrossRef] [PubMed]

65. Merota, M.; Tanji, Y.; Mizoguchi, K.; Akitsu, T.; Kijima, N.; Unno, H. Characterization of a Virulent Bacteriophage Specific for Escherichia coli O157:H7 and Analysis of Its Cellular Receptor and Two Tail Fiber Genes. FEMS Microbiol. Lett. 2002, 211, 77–83. [CrossRef] [PubMed]

66. Hudson, J.A.; Billington, C.; Cornelius, A.J.; Wilson, T.; On, S.L.W.; Premaratne, A.; King, N.J. Use of a Bacteriophage to Inactivate Escherichia coli O157:H7 on Beef. Food Microbiol. 2013, 36, 14–21. [CrossRef] [PubMed]

67. Kudva, I.T.; Jelacic, S.; Tarr, P.I.; Youderian, P.; Hovde, C.J. Biocontrol of Escherichia coli O157 with O157-Specific Bacteriophages. Appl. Environ. Microbiol. 1999, 65, 3767–3773. [CrossRef] [PubMed]

68. Sharma, M.; Ryu, J.-H.; Beuchat, L.-R. Inactivation of Escherichia coli O157:H7 in Biofilm on Stainless Steel by Treatment with an Alkaline Cleaner and a Bacteriophage. J. Appl. Microbiol. 2005, 99, 449–459. [CrossRef]

69. Abuladze, T.; Li, M.; Menetrez, M.Y.; Dean, T.; Senecal, A.; Sulakvelidze, A. Bacteriophages Reduce Experimental Contamination of Hard Surfaces, Tomato, Spinach, Broccoli, and Ground Beef by Escherichia coli O157:H7. Appl. Environ. Microbiol. 2008, 74, 6230–6238. [CrossRef]

70. Ferguson, S.; Roberts, C.; Handy, E.; Sharma, M. Lytic Bacteriophages Reduce Escherichia coli O157: H7 on Fresh Cut Lettuce Introduced through Cross-Contamination. Bacteriophage 2013, 3, e24323. [CrossRef]

71. Tomat, D.; Mercanti, D.; Balagué, C.; Quiberoni, A. Phage Biocontrol of Enteropathogenic and Shiga Toxin-Producing Escherichia coli during Milk Fermentation. Lett. Appl. Microbiol. 2013, 57, 3–10. [CrossRef]
72. Tomat, D.; Migliore, L.; Aquili, V.; Quiberoni, A.; Balagué, C. Phage Biocontrol of Enteropathogenic and Shiga Toxin-Producing Enterobacteriaceae in Meat Products. *Front. Cell Infect. Microbiol.* 2013, 3, 20. [CrossRef]

73. Snyder, A.B.; Perry, J.J.; Yousef, A.E. Developing and Optimizing Bacteriophage Treatment to Control Enterohemorrhagic *Escherichia coli* on Fresh Produce. *Int. J. Food Microbiol.* 2016, 236, 90–97. [CrossRef]

74. Deasy, T.; Mahony, J.; Neve, H.; Heller, K.J.; van Sinderen, D. Isolation of a Virulent *Lactobacillus brevis* Phage and Its Application in the Control of Beer Spoilage. *J. Food Prot.* 2011, 74, 2157–2161. [CrossRef] [PubMed]

75. Greer, G.G.; Dilts, B.D.; Ackermann, H.-W. Characterization of a *Leuconostoc gelidum* Bacteriophage from Pork. *Int. J. Food Microbiol.* 2007, 114, 370–375. [CrossRef]

76. Hibma, A.M.; Jassim, S.A.; Griffiths, M.W. Infection and Removal of L-Forms of *Listeria monocytogenes* by Bacteriophages. *Front. Cell Infect. Microbiol.* 2013, 3, e26861. [CrossRef] [PubMed]

77. Klumpp, J.; Loessner, M.J. Listeria Phages: Genomes, Evolution, and Application. *Bacteriophage* 2013, 3, 1987; pp. 49–85.

78. Zink, R.; Loessner, M.J. Classification of Virulent and Temperate Bacteriophages of *Listeria monocytogenes* by Listeriaphages and a Quaternary Ammonium Compound. *Appl. Environ. Microbiol.* 1993, 59, 2914–2917. [CrossRef] [PubMed]

79. Ackermann, H.W.; DuBow, M.S. Bacteriophage Biocontrol of *Listeria monocytogenes* on Fresh-Cut Fruits and Fruit Juices. *Appl. Environ. Microbiol.* 2008, 74, 93–100. [CrossRef]

80. Roy, B.; Ackermann, H.W.; Pandian, S.; Picard, G.; Goulet, J. Biological Inactivation of Adhering *Listeria monocytogenes* by Listeriaphages and a Quaternary Ammonium Compound. *Appl. Environ. Microbiol.* 1995, 61, 49–54. [CrossRef] [PubMed]

81. Guenther, S.; Loessner, M.J. Bacteriophage Biocontrol of *Listeria monocytogenes* in Raw Cow’s Milk. *Appl. Environ. Microbiol.* 2013, 79, 79. [CrossRef] [PubMed]

82. Soni, K.A.; Nannapaneni, R.; Hagens, S. Reduction of *Listeria monocytogenes* on Raw Salmon Fillet Tissue. *J. Food Prot.* 2010, 73, 32–38. [CrossRef]

83. Carlton, R.M.; Noordman, W.H.; Biswas, B.; de Meester, E.D.; Loessner, M.J. Bacteriophage P100 for Control of *Listeria monocytogenes* in Foods: Genome Sequence, Bioinformatic Analyses, Oral Toxicity Study, and Application. *Regul. Toxicol. Pharmacol.* 2005, 43, 301–312. [CrossRef]

84. Ellis, D.E.; Whitman, P.A.; Marshall, R.T. Effects of Homologous Bacteriophage on Growth of *Pseudomonas fragi* WY in Milk. *Appl. Microbiol.* 1973, 25, 24–25. [CrossRef]

85. Aprea, G.; D’Angelo, A.R.; Principe, V.A.; Migliorati, G. Bacteriophage Morphological Characterization by Using Transmission Electron Microscopy. *J. Life Sci.* 2015, 9, 214–220.

86. Bigot, B.; Lee, W.-J.; McIntyre, L.; Wilson, T.; Hudson, J.A.; Billington, C.; Heinemann, J.A. Control of *Listeria monocytogenes* Growth in a Ready-to-Eat Poultry Product Using a Bacteriophage. *Food Microbiol.* 2011, 28, 1448–1452. [CrossRef] [PubMed]

87. Aprea, G.; D’Angelo, A.R.; Principe, V.A.; Migliorati, G. Bacteriophage Morphological Characterization by Using Transmission Electron Microscopy. *J. Life Sci.* 2015, 9, 214–220.

88. Bigot, B.; Lee, W.-J.; McIntyre, L.; Wilson, T.; Hudson, J.A.; Billington, C.; Heinemann, J.A. Control of *Listeria monocytogenes* Growth in a Ready-to-Eat Poultry Product Using a Bacteriophage. *Food Microbiol.* 2011, 28, 1448–1452. [CrossRef] [PubMed]

89. Scattolini, S.; D’Angelantonio, D.; Boni, A.; Mangone, I.; Marcacci, M.; Battistelli, N.; D’Agostino, K.; Pomilio, F.; Camma, C.; Migliorati, G.; et al. Characterization and In Vitro Efficacy against *Listeria monocytogenes* of a Newly Isolated Bacteriophage, Φ1ZSM-1. *Microorganisms* 2021, 9, 731. [CrossRef]

90. Tanaka, C.; Yamada, K.; Takeuchi, H.; Inokuchi, Y.; Kashiwagi, A.; Toba, T. A Lytic Bacteriophage for Controlling *Pseudomonas lactis* in Raw Cow’s Milk. *Appl. Environ. Microbiol.* 2018, 84, e00111-18. [CrossRef] [PubMed]

91. Sillankorva, S.; Neubauer, P.; Azeredo, J. *Pseudomonas fluorescens* Biofilms Subjected to Phage PhIBB-PF7A. *BMC Biotechnol.* 2008, 8, 79. [CrossRef]
110. Huang, C.; Virk, S.M.; Shi, J.; Zhou, Y.; Willias, S.P.; Mia, M.Z.; Bei, W.; Connerton, I.F.; Fischetti, V.A.; et al. Application of a Broad Spectrum Lytic Phage LPST94 for Biological Control of Salmonella in Foods and Reducing Biofilms. Iran J. Vet. Res. 2019, 20, 413–426. [CrossRef] [PubMed]

111. Whichard, J.M.; Sriranganathan, N.; Pierson, F.W. Suppression of Salmonella Typhimurium in Foods: Characterization, Application, Sequence Analysis, and Oral Acute Toxicity Study. Appl. Environ. Microbiol. 2010, 76, 679–688. [CrossRef] [PubMed]

112. Whichard, J.M.; Kim, J.W.; Jung, T.-S.; Woo, G.-J. Wksl3, a New Biocontrol Agent for Salmonella Entercra Serovars Enteritidis and Typhimurium in Foods. Characterization, Application, Sequence Analysis, and Oral Acute Toxicity Study. Appl. Environ. Microbiol. 2013, 79, 1956–1968. [CrossRef]

113. Felix, A.; Callow, B.R. Typing of Paratyphoid B Bacilli by Vi Bacteriophage. Br. Med. J. 1943, 2, 127–130. [CrossRef] [PubMed]

114. Guenther, S.; Herzig, O.; Fieseler, L.; Klumpp, J.; Loessner, M.J. Biocontrol of Salmonella in Foods and Reducing Biofilms. Molecules 2021, 26, 5138. [CrossRef] [PubMed]

115. Higgins, J.P.; Higgins, S.E.; Guenther, K.L.; Huff, W.; Donoghue, A.M.; Donoghue, D.J.; Hargis, B.M. Use of a Specific Bacteriophage against Salmonella Typhimurium in RTE Foods with the Virulent Bacteriophage FO1-E2. Int. J. Food Microbiol. 2012, 154, 66–72. [CrossRef] [PubMed]

116. Wall, S.K.; Zhang, J.; Rostagno, M.H.; Ebner, P.D. Phage Therapy to Reduce Preprocessing Salmonella Infections in Market-Weight Swine. Appl. Environ. Microbiol. 2010, 76, 48–53. [CrossRef] [PubMed]

117. Zhang, J.; Hong, Y.; Harman, N.J.; Das, A.; Ebner, P.D. Genome Sequence of a Salmonella Phage Used to Control Salmonella Transmission in Swine. Genome Announc. 2014, 2, e00521-14. [CrossRef] [PubMed]

118. Hong, Y.; Schmidt, K.; Marks, D.; Hatter, S.; Marshall, A.; Albino, L.; Ebner, P. Treatment of Salmonella-Contaminated Eggs and Pork with a Broad-Spectrum, Single Bacteriophage: Assessment of Efficacy and Resistance Development. Foodborne Pathog. Dis. 2016, 13, 679–688. [CrossRef] [PubMed]

119. Zhang, Y.; Ding, Y.; Li, W.; Zhou, W.; Wang, J. Application of a Novel Lytic Podoviridiae Phage Pu20 for Biological Control of Drug-Resistant Salmonella in Liquid Eggs. Pathogens 2021, 10, 34. [CrossRef] [PubMed]

120. Li, Z.; Ma, W.; Li, W.; Ding, Y.; Zhang, Y.; Yang, Q.; Wang, J.; Wang, X. A Broad-Spectrum Phage Controls Multidrug-Resistant Salmonella in Liquid Eggs. Food Res. Int. 2020, 132, 109011. [CrossRef]

121. Ahn, J.; Kim, S.; Jung, L.-S.; Biswas, D. In Vitro Assessment of the Susceptibility of Planktonic and Attached Cells of Foodborne Bacteriophage P22-Mediated Salmonella Lysates. J. Food Prot. 2013, 76, 2057–2062. [CrossRef] [PubMed]

122. Susskind, M.M.; Botstein, D. Molecular Genetics of Bacteriophage P22. Microbiol. Rev. 1978, 42, 385–413. [CrossRef]

123. Zorn, G.A.; Gough, M. Morphology of Bacteriophage P22 as Seen in Thin Sections of Pelleted Phage. Virology 1976, 71, 434–443. [CrossRef]

124. Zinno, P.; Devirgiliis, C.; Ercolini, D.; Ongeng, D.; Mauriello, G. Bacteriophage P22 to Challenge Salmonella in Foods. Int. J. Food Microbiol. 2014, 191, 69–74. [CrossRef] [PubMed]

125. Islam, M.S.; Hu, Y.; Mizan, M.F.R.; Yan, T.; Nime, I.; Zhou, Y.; Li, J. Isolation, Characterization of a T7-like Lytic Phage LPST153 That Effectively Targets Most Prevalent Salmonella Serovars. Microorganisms 2020, 8, 1089. [CrossRef]

126. Spricigo, D.A.; Bardina, C.; Cortés, P.; Llagostera, M. Use of a Bacteriophage Cocktail to Control Salmonella Enteritidis in Chicken Breast Meat. J. Food Sci. 2020, 85, 526–534. [CrossRef]

127. Bardina, C.; Colom, J.; Spricigo, D.A.; Otero, J.; Sánchez-Osuna, M.; Cortés, P.; Llagostera, M. Genomics of Three New Bacteriophages Useful in the Biocontrol of Salmonella. Front. Microbiol. 2016, 7, 545. [CrossRef] [PubMed]
129. Augustine, J.; Bhat, S.G. Biocontrol of Salmonella Enteritidis in Spiked Chicken Cuts by Lytic Bacteriophages ΦSP-1 and ΦSP-3. *J. Basic Microbiol.* 2015, 55, 500–503. [CrossRef] [PubMed]
130. Augustine, J.; Varghese, S.M.; Bhat, S.G. ΦSP-3, a Salmonella-Specific Lytic Phage Capable of Infecting Its Host under Nutrient-Deprived States. *Ann. Microbiol.* 2013, 63, 381–386. [CrossRef]
131. Modi, R.; Hirvi, Y.; Hill, A.; Griffiths, M.W. Effect of Phage on Survival of Salmonella Enteritidis during Manufacture and Storage of Cheddar Cheese Made from Raw and Pasteurized Milk. *J. Food Prot.* 2001, 64, 927–933. [CrossRef]
132. Bao, H.; Zhang, P.; Zhang, H.; Zhou, Y.; Zhang, L.; Wang, R. Bio-Control of Salmonella Enteritidis in Foods Using Bacteriophages. *Viruses* 2015, 7, 4836–4853. [CrossRef]
133. Bao, H.; Zhou, Y.; Shahin, K.; Zhang, H.; Cao, F.; Pang, M.; Zhang, X.; Zhu, S.; Olaniran, A.; Schmidt, S.; et al. The Complete Genome of Lytic Salmonella Phage VB_SenM-PA13076 and Therapeutic Potency in the Treatment of Lethal Salmonella Enteritidis Infections in Mice. *Microbiol. Res.* 2020, 237, 126471. [CrossRef] [PubMed]
134. Duc, H.M.; Son, H.M.; Yi, H.P.S.; Sato, J.; Ngan, P.H.; Masuda, Y.; Honjoh, K.-I.; Miyamoto, T. Isolation, Characterization and Application of a Polyvalent Phage Capable of Controlling Salmonella and Escherichia coli O157:H7 in Different Food Matrices. *Food Res. Int.* 2020, 131, 108977. [CrossRef]
135. Kocharunchitt, C.; Ross, T.; McNiel, D.L. Use of Bacteriophages as Biocontrol Agents to Control Salmonella Associated with Seed Sprouts. *Int. J. Food Microbiol.* 2009, 138, 23–27. [CrossRef] [PubMed]
136. Pao, S.; Rolph, S.P.; Westbrook, E.W.; Shen, H. Use of Bacteriophages to Control Salmonella in Experimentally Contaminated Sprout Seeds. *J. Food Sci.* 2006, 69, 123–130. [CrossRef] [PubMed]
137. Li, J.; Li, Y.; Ding, Y.; Huang, C.; Zhang, Y.; Wang, J.; Wang, X. Characterization of a Novel Siphoviridae Salmonella Bacteriophage TiS6 and Its Microencapsulation Application in Food Matrix. *Food Res. Int.* 2021, 140, 110004. [CrossRef] [PubMed]
138. Kelly, D.; McAuliffe, O.; Ross, R.P.; Cotley, A. Prevention of *Staphylococcus aureus* Biofilm Formation and Reduction in Established Biofilm Density Using a Combination of Phage K and Modified Derivatives. *Lett. Appl. Microbiol.* 2012, 54, 286–291. [CrossRef] [PubMed]
139. Gill, J.J. Revised Genome Sequence of *Staphylococcus aureus* Bacteriophage K. *Genome Announce.* 2014, 2, e01173-13. [CrossRef]
140. Bueno, E.; Garcia, P.; Martinez, B.; Rodriguez, A. Phage Inactivation of *Staphylococcus aureus* in Fresh and Hard-Type Cheeses. *Int. J. Food Microbiol.* 2012, 158, 23–27. [CrossRef]
141. Garcia, P.; Madera, C.; Martinez, B.; Rodriguez, A. Biocontrol of *Staphylococcus aureus* in Curd Manufacturing Processes Using Bacteriophages. *Int. J. Dairy* 2007, 17, 1232–1239. [CrossRef] [PubMed]
142. Garcia, P.; Martinez, B.; Obeso, J.M.; Lavigne, R.; Lurz, R.; Rodriguez, A. Functional Genomic Analysis of Two *Staphylococcus aureus* Phages Isolated from the Dairy Environment. *Appl. Environ. Microbiol.* 2009, 75, 7663–7673. [CrossRef] [PubMed]
143. Duc, H.M.; Son, H.M.; Ngan, P.H.; Sato, J.; Masuda, Y.; Honjoh, K.-I.; Miyamoto, T. Isolation, Characterization and Application of Bacteriophages Alone or in Combination with Nisin against Planktonic and Biofilm Cells of *Staphylococcus aureus*. *Appl. Microbiol. Biotechnol.* 2020, 104, 5145–5158. [CrossRef] [PubMed]
144. Chang, Y.; Bai, J.; Lee, J.-H.; Ryu, S. Mutation of a *Staphylococcus aureus* Temperate Bacteriophage to a Virulent One and Evaluation of Its Application. *Food Microbiol.* 2019, 82, 523–532. [CrossRef] [PubMed]
145. Yang, Z.-Q.; Tao, X.-Y.; Zhang, H.; Rao, S.-Q.; Gao, L.; Pan, Z.-M.; Jiao, X.-A. Isolation and Characterization of Virulent Phages Infecting *Shewanella baltica* and *Shewanella putrefaciens*, and Their Application for Biopreservation of Chilled Channel Catfish (Ictalurus punctatus). *Int. J. Food Microbiol.* 2019, 292, 107–117. [CrossRef] [PubMed]
146. Zhang, H.; Wang, R.; Bao, H. Phage Inactivation of Foodborne *Shigella* on Ready-to-Eat Spiced Chicken. *Poult. Sci.* 2013, 92, 211–217. [CrossRef]
147. Zhang, H.; Yang, Z.; Zhou, Y.; Bao, H.; Wang, R.; Li, T.; Pang, M.; Sun, L.; Zhou, X. Application of a Phage in Decontaminating *Vibrio parahaemolyticus* in Oysters. *Int. J. Microbiol.* 2018, 275, 24–31. [CrossRef]
148. Cooper, I.R. A Review of Current Methods Using Bacteriophages in Live Animals, Food and Animal Products Intended for Human Consumption. *J. Microbiol. Methods* 2016, 130, 38–47. [CrossRef] [PubMed]
149. Gray, J.A.; Chandry, P.S.; Kaur, M.; Kocharunchitt, C.; Bowman, J.P.; Fox, E.M. Novel Biocontrol Methods for *Listeria monocytogenes* Biofilms in Food Production Facilities. *Front. Microbiol.* 2018, 9, 605. [CrossRef]
150. Hsu, F.C.; Shieh, Y.S.C.; Sobsey, M.D. Enteric Bacteriophages as Potential Fecal Indicators in Ground Beef and Poultry Meat. *J. Food Prot.* 2002, 65, 93–99. [CrossRef] [PubMed]
151. Wongsuphantnopj, S.; Moreno Switt, A.I.; Bergholz, P.; Wiedmann, M.; Chaturongakul, S. *Salmonella* Phages Isolated from Dairy Farms in Thailand Show Wider Host Range than a Comparable Set of Phages Isolated from U.S. Dairy Farms. *Int. J. Food Microbiol.* 2017, 211–217. [CrossRef] [PubMed]
152. Muniesa, M.; Jofre, J. Abundance in Sewage of Bacteriophages Infecting *Escherichia coli* O157:H7. *Methods Mol. Biol.* 2004, 268, 79–88. [CrossRef]
153. DePaola, A.; Motes, M.L.; Chan, A.M.; Suttle, C.A. Phages Infecting *Vibrio vulnificus* Are Abundant and Diverse in Oysters (*Crassostrea virginica*) Collected from the Gulf of Mexico. *Appl. Environ. Microbiol.* 1998, 64, 346–351. [CrossRef]
154. Munain-Mujika, I.; Calvo, M.; Lucena, F.; Girones, R. Comparative Analysis of Viral Pathogens and Potential Indicators in Shellfish. *Int. J. Food Microbiol.* 2003, 83, 75–85. [CrossRef] [PubMed]
155. Leclerc, H.; Edberg, S.; Pierzo, V.; Delattre, J.M. Bacteriophages as Indicators of Enteric Viruses and Public Health Risk in Groundwaters. *J. Appl. Microbiol.* 2000, 88, 5–21. [CrossRef]
189. Fenton, M.; Keary, R.; McAuliffe, O.; Ross, R.P.; O’Mahony, J.; Coffey, A. Bacteriophage-Derived Peptidase CHAP(K) Eliminates and Prevents Staphylococcal Biofilms. *Int. J. Microbiol.* 2013, 2013, 625341. [CrossRef]

190. Gutiérrez, D.; Ruas-Madiedo, P.; Martínez, B.; Rodríguez, A.; García, P. Effective Removal of Staphylococcal Biofilms by the Endolysin LysH5. *PLoS ONE* 2014, 9, e107307. [CrossRef]

191. Sass, P.; Bierbaum, G. Lytic Activity of Recombinant Bacteriophage Phi11 and Phi12 Endolysins on Whole Cells and Biofilms of *Staphylococcus aureus*. *Environ. Microbiol.* 2007, 9, 347–352. [CrossRef] [PubMed]

192. Son, J.-S.; Lee, S.-J.; Jun, S.Y.; Yoon, S.J.; Kang, S.H.; Paik, H.R.; Kang, J.O.; Choi, Y.-J. Antibacterial and Biofilm Removal Activity of a *Podoviridae* *Staphylococcus aureus* Bacteriophage SAP-2 and a Derived Recombinant Cell-Wall-Degrading Enzyme. *Appl. Microbiol. Biotechnol.* 2010, 86, 1439–1449. [CrossRef] [PubMed]

193. Gerstmanns, H.; Criel, B.; Briers, Y. Synthetic Biology of Modular Endolysins. *Biotechnol. Adv.* 2018, 36, 624–640. [CrossRef]

194. Yang, H.; Yu, J.; Wei, H. Engineered Bacteriophage Lysins as Novel Anti-Infectives. *Front. Microbiol.* 2014, 5, 542. [CrossRef]

195. Son, B.; Kong, M.; Cha, Y.; Bai, J.; Ryu, S. Simultaneous Control of *Staphylococcus aureus* and *Bacillus cereus* Using a Hybrid Endolysin LysB4EAD-LysSA11. *Antibiotics* 2020, 9, 906. [CrossRef]

196. Son, B.; Yun, J.; Lim, J.-A.; Shin, H.; Heu, S.; Ryu, S. Characterization of LysB4, an Endolysin from the *Bacillus cereus*-Infesting Bacteriophage B4. *BMC Microbiol.* 2012, 12, 33. [CrossRef] [PubMed]

197. Garde, S.; Calzada, J.; Sánchez, C.; Gaya, P.; Narbad, A.; Meijers, R.; Mayer, M.J.; Ávila, M. Effect of *Lactococcus lactis* Expressing Phage Endolysin on the Late Blowing Defect of Cheese Caused by *Clostridium tyrobutyricum*. *Int. J. Food Microbiol.* 2020, 329, 108686. [CrossRef]

198. Mayer, M.J.; Casson, M.J.; Narbad, A. Genomic Sequence of Bacteriophage ATCC 8074-B1 and Activity of Its Endolysin and Engineered Variants against *Clostridium sporogenes*. *Appl. Environ. Microbiol.* 2012, 78, 3685–3692. [CrossRef]

199. Zimmer, M.; Vukov, N.; Scherer, S.; Loessner, M.J. The Murein Hydrolase of the Bacteriophage Phi3626 Dual Lysis System Is Active against All Tested *Clostridium perfringens* Strains. *Appl. Environ. Microbiol.* 2002, 68, 5311–5317. [CrossRef]

200. Cho, J.-H.; Kwon, J.-G.; O’Sullivan, D.J.; Ryu, S.; Lee, J.-H. Development of an Endolysin Enzyme and Its Cell Wall-Binding Domain Protein and Their Applications for Biocontrol and Rapid Detection of *Clostridium perfringens* in *Food*. *Food Chem.* 2021, 345, 128562. [CrossRef] [PubMed]

201. Loessner, M.J.; Wendlinger, G.; Scherer, S. Heterogeneous Endolysins in *Listeria monocytogenes* Bacteriophages: A New Class of Enzymes and Evidence for Conserved Holin Genes within the Siphoviral Lysis Cassettes. *Mol. Microbiol.* 1995, 16, 1231–1241. [CrossRef] [PubMed]

202. Gaeng, S.; Scherer, S.; Neve, H.; Loessner, M.J. Gene Cloning and Expression and Secretion of *Listeria monocytogenes* Bacteriophage-Lytic Enzymes in *Lactococcus lactis*. *Appl. Microbiol. Biochem.* 2000, 66, 2951–2958. [CrossRef]

203. Turner, M.S.; Waldherr, F.; Loessner, M.J.; Giffard, P.M. Antimicrobial Activity of Lysostaphin and a *Listeria monocytogenes* Bacteriophage Endolysin Produced and Secreted by Lactic Acid Bacteria. *Syst. Appl. Microbiol.* 2007, 30, 58–67. [CrossRef] [PubMed]

204. Xu, S.; Campisi, E.; Li, J.; Fischetti, V.A. Decontamination of *Escherichia coli* O157:H7 on Fresh Romaine Lettuce Using a Novel Bacteriophage Lysin. *Int. J. Food Microbiol.* 2021, 341, 109068. [CrossRef] [PubMed]

205. Ribelles, P.; Rodríguez, I.; Suárez, J.E. LysA2, the *Lactobacillus casei* Bacteriophage A2 Lysin Is an Endopeptidase Active on a Wide Spectrum of Lactic Acid Bacteria. *Appl. Microbiol. Biotechnol.* 2012, 94, 101–110. [CrossRef]

206. Van Tassell, M.L.; Ibarra-Sánchez, L.A.; Hoeper, G.P.; Miller, M.J. Hot Topic: Antilisterial Activity by Endolysin PlyP100 in Fresh Cheese. *J. Dairy Sci.* 2017, 100, 2482–2487. [CrossRef]

207. Zhang, H.; Bao, H.; Billington, C.; Hudson, J.A.; Wang, R. Isolation and Lytic Activity of the *Listeria* Bacteriophage Endolysin LysZ5 against *Listeria monocytogenes* in Soya Milk. *Food Microbiol.* 2012, 31, 133–136. [CrossRef] [PubMed]

208. Simmons, M.; Morales, C.A.; Oakley, B.B.; Seal, B.S. Recombinant Expression of a Putative Amidase Cloned from the Genome of *Listeria monocytogenes* That Lyses the Bacterium and Its Monolayer in Conjunction with a Protease. *Probiotics Antimicrob. Proteins* 2012, 4, 1–10. [CrossRef] [PubMed]

209. Schmelcher, M.; Waldherr, F.; Loessner, M.J. *Listeria* Bacteriophage Peptidoglycan Hydrolases Feature High Thermoresistance andReveal Increased Activity after Divalent Metal Cation Substitution. *Appl. Microbiol. Biotechnol.* 2012, 93, 633–644. [CrossRef]

210. Dorscht, J.; Klumpp, J.; Bielmann, R.; Schmelcher, M.; Born, Y.; Zimmer, M.; Calendar, R.; Loessner, M.J. Comparative Genome Analysis of *Listeria* Bacteriophages Reveals Extensive Mosaicism, Programmed Translational Frameshifting, and a Novel Prophage Insertion Site. *J. Bacteriol.* 2009, 191, 7206–7215. [CrossRef] [PubMed]

211. Yan, J.; Yang, R.; Yu, S.; Zhao, W. The Application of the Lytic Domain of Endolysin from *Staphylococcus aureus* Bacteriophage in Milk. *J. Dairy Sci.* 2021, 104, 2641–2653. [CrossRef]

212. Gu, J.; Xu, W.; Lei, L.; Huang, J.; Feng, X.; Sun, C.; Du, C.; Zuo, J.; Li, Y.; Du, T.; et al. LysGH15, a Novel Bacteriophage Lysin, Protects a Murine Bacteremia Model Efficiently against Lethal Methicillin-Resistant *Staphylococcus aureus* Infection. *J. Clin. Microbiol.* 2011, 49, 111–117. [CrossRef]

213. Chang, Y.; Kim, M.; Ryu, S. Characterization of a Novel Endolysin LysSA11 and Its Utility as a Potent Biocontrol Agent against *Staphylococcus aureus* on Food and Utensils. *Food Microbiol.* 2017, 68, 112–120. [CrossRef] [PubMed]

214. García, P.; Martínez, B.; Rodríguez, L.; Rodríguez, A. Synergy between the Phage Endolysin LysH5 and Nisin to Kill *Staphylococcus aureus* in Pasteurized Milk. *Int. J. Food Microbiol.* 2010, 141, 151–155. [CrossRef] [PubMed]
