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Review

The use of bacteriophages in food safety and pathogen control. Review

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Abstract:

The increase in human population will be directly proportional to the demand for food that must meet the global requirements, which implies the urgency of ensuring food quality, maintaining its attributes and nutritional values without contributing to increase bacterial resistance. In recent years, bacteriophages have gained relevance due to their high specificity and to their being regarded as environmentally friendly for the biological control of pathogens in food. Multiple scientific evidence has revealed a great effectiveness of bacteriophages in significantly decreasing the bacterial count of pathogens associated with the food industry. Moreover, in recent years, several international companies have begun to produce and commercialize phage-based products for application in food products. This review highlights recent research on the use of bacteriophages in raw or cooked meat from different animals, ready-to-eat foods, food handling surfaces, and packaging materials to combat foodborne pathogens most frequently reported in outbreaks, including *Salmonella*, *Escherichia coli*, *Campylobacter*, and *Listeria monocytogenes.* In addition, phage products that are marketed by several companies for use in food decontamination are mentioned.

Keywords: Bacteriophages, Decontamination, Food safety, Pathogens, Decontamination, Food safety.

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Introduction

The ingestion of food and water contaminated with pathogenic microorganisms can give rise to more than 200 infectious diseases and is considered one of the major causes of hospitalizations and deaths worldwide[1]. *Salmonella* spp., *Campylobacter* spp., *E. coli, L. monocytogenes*, and *Yersinia* spp. are the main bacterial pathogens reported in infectious cases due to food consumption. Given their ubiquity, antibiotic resistance, biofilm formation, ability to grow in hostile environments, virulence factors, and pathogenicity, these pathogens are of great interest to the public health sector[2]. According to World Health Organization (WHO) estimates, 600 million people annually experience an infectious event related to contaminated food, resulting in more than 420,000 deaths[3]. Within this context, it is essential to prevent, detect, and control food contamination to ensure the safety of food intended for human consumption[2].

Currently, there are several methods of food disinfection; however, not all of them are applicable to all products. For example, heat treatment can eliminate microflora in food[4]; pasteurization is not recommended for fresh produce and meat, as it can affect the organoleptic properties and nutritional content of the products. Ionizing radiation can alter the appearance of foods and thus decrease consumer acceptance[5], and chemical disinfectants are linked to health problems such as cancer, asthma, and neurological damage[6]. Therefore, it is essential to identify and develop effective alternatives for the control of foodborne diseases that are environmentally friendly and provide consumer safety. One solid option is biocontrol with bacteriophages[2].

Bacteriophages (phages) are viruses that exclusively infect bacteria, being specific towards certain species or even certain strains[7]. Their specificity is one of their most attractive characteristics, since they offer a unique opportunity to eliminate specific bacteria from the food without altering its natural microflora and organoleptic properties, favoring them over antibiotics and chemical agents[8,9]. In recent years, phages have gained acceptance as a natural and green technology, given that many commercialized phage products contain no

additives and are internationally certified[5], meeting consumer demands for foods that are free of chemical preservatives, minimally processed, and naturally produced[3].

Seeking innovative solutions that ensure food security while maintaining high standards of food production is key to social, economic, and health development. This review, summarize and discuss recent findings that expose the potential of bacteriophages to be used as biocontrol for pathogen reduction in food products of animal origin, ensuring consumer safety.

Bacteriophages

Bacteriophages are the most abundant biological entities on the planet, adding up to approximately10^{31} particles[10]. These are found in all ecosystems where bacteria are present. They play a crucial role in the microbiological balance, as they are estimated to eliminate half of the world's bacterial population every 48 h[10]. In addition, they significantly reduce bacterial colonization in humans and animals, acting as an additional component of innate immunity[11], and play an important role in the intestinal microbiota[10].

The term “bacteriophage” comes from the Greek words “bacteria” and “phage”, meaning “bacteria-eater”. It was first introduced to the scientific community in 1917 by Félix d'Herelle, who began to administer them therapeutically for various bacterial infections[12]. However, in previous years, several studies already suggested a phage action; for example, in 1847, Ernest H. Hankin reported an unusual antibacterial activity in the Yamuna and Ganges rivers, proposing their ingestion to reduce *Vibrio Cholerae*, the cause of the cholera epidemic. Similarly, in 1915, Frederick W. Twort observed lytic activity in a pure culture of *Micrococcus*, raising the hypothesis of an ultramicroscopic virus; unfortunately, due to social and economic conflicts, he was unable to confirm or refute his hypothesis[8].

Depending on the infection cycle, two types of phages can be distinguished. Temperate bacteriophages, which carry out a lysogenic cycle, represent a safety risk due to their ability to horizontally transfer resistance genes and virulence factors. On the other hand, lytic (also called virulent) bacteriophages are ideal for the biocontrol of food-related pathogens due to their infection cycle. After inserting their genetic material and taking control of the bacterial replication machinery, new virions are formed and released into the environment by lysis[13]. Phages have a high degree of selectivity to infect and kill specific bacteria, being harmless to humans and animals, which makes them an attractive alternative to the use of antibiotics[3].

The tendency towards the consumption of chemical-free, safe, and acceptable foods has been increasing over the past two decades, accelerating markedly due to the COVID-19 pandemic[14,15]. Therefore, several phage preparations composed of one or several phages (cocktails) have been approved by the Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA), gaining importance for their ecological approach and considering them environmentally friendly. Also for their potential to be used in different stages of food production such as cleaning of facilities, disinfection of industrial equipment, preservatives, and biocontrol in raw and cooked foods without affecting their sensory properties and nutritional values[2,4].

Foodborne pathogens

Salmonella

Salmonella is a Gram-negative zoonotic pathogen that belongs to the family *Enterobacteriacea.* Chickens are the most common hosts of this pathogen, followed by cattle, turkeys, pigs, ducks, and geese[13]. This microorganism is responsible for diarrheal diseases in humans, which manifest themselves with symptoms such as abdominal pain and headache, cramps, nausea, vomiting, diarrhea, fever, and dehydration. In severe cases, they can lead to death[4].

Salmonella transmission occurs mainly after consuming water and foods of animal and vegetable origin that have been contaminated. For example, in 2023, one study reported a prevalence of ~50% of *Salmonella* spp. in pork sausages and chicken and turkey breast fillets, ~25% in chicken eggs and seafood, and ~10% in beef. Worldwide, *Salmonella* is the third most common cause of human death among diarrheal diseases[1]. According to global estimates, non-typhoidal *Salmonella* accounts for 93.8 million enteric infections and 155,000 human deaths per year[13]. *Salmonella* Enteritidis and *Salmonella* Typhimurium serovars are particularly relevant to public health, as they are the most prevalent serovars in food that cause outbreaks in humans[8].

The efficacy of bacteriophages in the control of *Salmonella* spp. in food for human consumption has been corroborated in multiple researches (Table 1). A recent study highlighted the effectiveness of PhageGuard S® phage cocktail in eliminating *Salmonella* Enteritidis in raw chicken meat samples purchased from local stores. During the course of the experiment, the samples were artificially contaminated with 10^4 CFU/cm^2 and, after 30 min, were treated with 1-2 x10^7 PFU/cm^2 of the cocktail. Bacterial counts decreased

significantly to 1.5 log units in the first 24 h; no further reduction was observed thereafter, suggesting a short phage action time[16]. Similarly, another study to assess this same phage product in combination with ultraviolet light determined that, at a final concentration of 10^9 PFU/mL and after 1.5 h of its application to ground beef artificially inoculated with 3.5 $\log_{10}$ CFU/g of *Salmonella* spp., the bacterial count decreased by approximately 2 logarithmic units compared to the control group[17].

In addition, samples of cold turkey meat, sausages, and seafood were deliberately contaminated with a concentration of 1 x 10^3 of *S.* Typhimurium and were exposed to 3 x 10^8 PFU/g of the FO1-E2 phage. After six days of storage at 8 ºC, no viable bacterial counts were recorded, demonstrating the efficacy of phages as a biocontrol tool in ready-to-eat foods[18].

Another study found that the application of a phage cocktail (composed of 5 phages) with a concentration of 9 log10 PFU/g, compared to the control group with 5.9 and 3.1 CFU/g, significantly reduced the count of *S.* Enteritidis in raw salmon samples by 3.2 and 2.8 log units (CFU/g) after storage at 18 and 4 ºC, respectively, for 10 d. In addition, under similar storage conditions, smoked salmon samples showed a reduction of 1.9 and 1.2 log units (CFU/g), compared to the control group, with a count of 6.9 and 2.2 CFU/g, respectively. This is evidence of the efficacy of this cocktail in reducing *Salmonella* contamination in food products of aquatic origin[19].

Similarly, after 24 h of administration of the SJ2 environmental phage at a concentration of 10^8 PFU/mL, a significant reduction of 1.65 and 3.14 $\log_{10}$ CFU/mL of *S.* Typhimurium was detected in samples of ground pork and liquid egg, respectively, stored at room temperature and artificially inoculated with 10^7 CFU/mL of *S.* Typhimurium[20].

On the other hand, research evaluated the efficacy of a cocktail of three phages (isolated from the environment) for the elimination of biofilm formed by a mixture of *S.* Typhimurium and *S.* Enteritidis on stainless steel surfaces. Phage titer of 7-8 log10 PFU/cm^2 significantly decreased ~5.5 log units of bacterial count compared to the control (~9 $\log_{10}$ CFU/cm^2), suggesting that phages can be used to disinfect equipment related to food processing and thus reduce the risk of cross-contamination[21].

Phages have also been shown to be an excellent option for food preservation. In a recent experiment, a cocktail of six phages (10^9 PFU/mL) was added to an absorbent pad used in refrigerated meat trays. The cocktail remained viable for 48 h at a temperature of 10-15 ºC. This treatment resulted in a significant reduction of *Salmonella enterica* serovar Typhimurium of 4.3 log CFU/mL, while the control group presented 9.8 CFU/mL[22]. Multiple evidence suggests that bacteriophages are an effective tool for extending the shelf life of refrigerated ready-to-eat foods[23].

Listeria monocytogenes

It is a Gram-positive, anaerobic, and zoonotic pathogen, whose main reservoirs are herd animals. This pathogen can also be found in soil and water contaminated by organic waste, where it has the ability to survive for more than 290 d[36].

Listeriosis, a disease caused by this pathogen, constitutes a serious public health problem. It is characterized by a high mortality rate of 25-30 %[4], with pregnant women, newborns, immunocompromised persons, and the elderly being the most vulnerable[1]. The main route of transmission to humans is through consumption of food contaminated with the bacteria, such as unpasteurized milk and cheeses, undercooked meat, ready-to-eat products such as sausages and pâté, and poorly washed fruits and vegetables. However, several studies have reported cross-contamination in products and utensils[10].

Infection manifests with fever, muscle pain, and gastrointestinal disorders (diarrhea and vomiting), which may progress to encephalitis, meningitis, loss of balance, and convulsions. In pregnant women, it can cause fetal death[4,8,9].

This pathogen has the ability to survive and multiply at refrigeration temperatures (2-8 ºC) for long periods of time, which favors its proliferation during food transportation and storage[9]. In addition, it can withstand similar conditions to those of food preparation, such as high salt levels, pH below 6, and absence of oxygen[8]. Therefore, it is of utmost importance to diagnose and eradicate this bacterium to ensure food safety, especially in ready-to-eat foods.

Current research confirms the high efficacy of bacteriophages against *L. monocytogenes* in ready-to-eat foods, in raw and cooked meat, and on surfaces used in food preparation (Table 2).

In 2017, research highlighted the efficacy of Listex™ P100 (1.5 x107 PFU/mL), a cocktail composed of 6 specific phages, endorsed by the FDA and with favorable opinions from the European Food Safety Authority (EFSA). This compound, applied to ready-to-eat slices of ham (approximately 30 g), was able to reduce to undetectable levels 2.83 log CFU/mL of experimentally inoculated L. *monocytogenes* serotype 1/2a. After 72 h of storage at refrigeration temperature (6 to 8 ºC), the phage product showed superior results compared to nisin and sodium lactate, which showed a reduction of 1.67 and 1.13 $\log_{10}$ CFU/g, respectively[37].

In another study, Listex™ P100 with a phage titer of 2.5 x 109 PFU/g was able to reduce approximately 2 log units of bacterial count in artisanal cheeses (Minas Frescal and Coalho) artificially contaminated with 10^5 CFU/g of a mixture of *L. monocytogenes* serotype 1/2a and ScottA, compared to the control group (~6 $\log_{10}$ PFU/g). The cheeses were stored for 30 min at 10 ºC[38]. In addition, in combination with enterocin AS-48 (0.37µg/cm2), Listex™ P100 recorded better results compared to single administration, as it maintained the bacterial count of a cocktail of five strains of *L. monocytogenes* (10^3 CFU/cm^2) inoculated *in vitro* in hake and raw and smoked salmon fillets, stored at 4 ºC, at undetectable levels. The antibacterial effect lasted from 7 to 15 h[39].

Several studies have confirmed the effectiveness of Listex™ P100 for the control of biofilms formed by *L. monocytogenes* in food production facilities. The application of the phage product on stainless steel surfaces has achieved a significant reduction in the bacterial count[40], diminishing it by up to 5 logarithmic units compared to the control[41]. This makes it a suitable option to reduce the risk of cross-contamination.

Similarly, the shelf life of the Listex™ P100 product (2 x 10^7 PFU/g) was maintained for 10 d at 4 and 10 °C, reducing by ~2 log units a count of ~4.3 $\log_{10}$ CFU/g in a mixture of *L. monocytogenes* serotypes 1/2a and 4b artificially inoculated into raw catfish fillets[42]. Moreover, 10^8 PFU/g of the same phage product reduced to 1.8-3.5 $\log_{10}$ CFU/g the mixture of *L. monocytogenes* serotypes 1/2a and 4b, with an initial load of 2-4 log CFU/g, in raw salmon fillets stored for 2 h at 4 and 22 ºC[43]. In a scientific opinion issued by the European Commission, it was reported that the dosage of Listex™ P100 used in ready-to-eat foods will reflect in the magnitude of the log reduction of *L. monocytogenes*. A phage titer of 10^9 PFU/cm^2 is estimated to reduce 2.52, 1.74, and 3.42 $\log_{10}$ CFU in fish, meat, and ready-to-eat dairy products, respectively[44].

The growth of *L. monocytogenes* strains 1/2a and ScottA when challenged with phage A511 (3 x 10^8 PFU/g) was monitored in ready-to-eat food samples highly sensitive to contamination. In hotdog samples, the phage neutralized the growth of strain 1/2a and reduced the ScottA strain of *L. monocytogenes* by 2.9 log units compared to the 10^4 CFU/g control group. In milk and mozzarella cheese samples, it eliminated both strains. In smoked salmon, there was no significant reduction of strain 1/2a; however, with respect to the control group (~10^4 CFU/g), there was a 2.2 log reduction of the ScottA strain. In shellfish samples with a control group, the use of ~10^5 CFU/g of serotype 1/2a and ~10^6 CFU/g of *L. monocytogenes* serotype ScottA reportedly brought 29% about a reduction of 1.5 and 2.5 log units, respectively[45].

The use of bacteriophages is an innovative antibacterial strategy to reduce the bacterial load on meat surfaces. For example, the commercial phage product ListShield™ was applied to decontaminate surfaces of raw meat samples that were artificially inoculated with *L.*

monocytogenes and stored for 15 d at 4 ºC. After the treatment, the pH and meat color values were not affected and the bacterial counts were significantly reduced by 2.3 log units compared to the control group (5.7 $\log_{10}$ CFU/g)[46]. This same phage agent with a titer of 10^7 PFU/cm^2 was able to eradicate the biofilm formed on the stainless-steel surface contaminated by ~10^6 CFU of *L. monocytogenes.* In addition, at a high contamination dose (10^5 CFU/mL) it reduced 3.5 log units, and at a low dose (10^3 CFU/mL) it achieved a complete elimination of the pathogen on cured ham surfaces stored at 4 ºC for 14 d[41].

Furthermore, it was demonstrated that a phage cocktail (10^9 PFU/mL) immobilized on a cellulose membrane was able to reduce the bacterial load of *L. monocyt*ogenes C391 strain (10^3 CFU/mL) to undetectable levels in roasted turkey breast samples preserved at 4 ºC. The efficacy of the treatment was maintained for up to 6 d in samples under aerobic conditions, one day in samples packaged in modified atmosphere, and 3 d in vacuum-packaged samples[47].

Escherichia coli

E. coli is a Gram-negative and facultative anaerobic bacillus. Although most strains of this enterobacterial species are ubiquitous and commensal in their hosts, playing beneficial mutualistic roles, a wide variety of pathogenic strains have been identified that can cause severe gastrointestinal disease[9]. These pathogenic strains can be classified into two pathotypes according to their virulence factors: Enteric pathogenic *E. coli* (EPEC), which includes enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), shiga toxin-producing *E. coli* (STEC), and enterohemorrhagic *E. coli* (EHEC); and the second group is extraintestinal pathogenic *E. coli* (ExPEC)[13]. STEC strains — among which serotypes O104:H4, O157, O103, O26, and O111 stand out— and, to a lesser extent, EPEC and ETEC strains are the most frequently associated with food poisoning outbreaks[56].

This pathogen can be found in contaminated environments such as water and soil, as well as in humans and animals. Its transmission to humans is generally due to the consumption of contaminated or undercooked food, such as meat products (chicken, beef), dairy products, juices, water, fruits and vegetables. Cross-contamination due to improper food handling has also been highlighted[57]. A high infective dose (10^3-10^6) is not required before hosts begin to manifest symptoms of infection, such as watery diarrhea, vomiting, fever, abdominal pain, nausea, and in more extreme cases, sepsis, hemolytic uremic syndrome, hemorrhagic colitis, and meningitis[8,57]. Although *E. coli* infection can occur at any age, immunocompromised persons, children under 5 yr of age, and the elderly are most vulnerable to a fatal outcome[8].

Several research studies have demonstrated the effectiveness of bacteriophages as biocontrol tools used in food (Table 3). In 2012, the efficacy of EcoShiel PX™, a commercial product composed of three phages, was evaluated, approved by the FDA and widely used to combat a wide range of STEC strains. During the experiment, samples of ground beef were artificially contaminated with 2 x 10^3 CFU/g of *E. coli* O157:H7, then treated (via spray) with 3 x 10^6 PFU/g of the phage cocktail and stored at 4 ºC. At 5 min, the bacterial count was reduced by 94 % with respect to the control (~4.5 x 10^3 CFU/g); this same level of reduction was maintained for 7 d; however, it did not show efficacy in a recontamination[58].

Another study reaffirming the efficacy of EcoShiel PX™ was conducted in 2020 when spraying 10^7 PFU/g of the cocktail reduced bacterial counts by 67 % in roast beef samples, 49 % in ground beef, 80 % in raw chicken breast, 69 % in cooked chicken, 80 % in raw salmon and 97 % in Cheddar cheese. The samples were experimentally inoculated with 3 log CFU/g O157:H7[59].

A group of researchers administered an MOI of 100 of the DW-EC phage (isolated from Dawet, a traditional Indonesian food) to treat chicken and fish meat samples that were purchased from supermarkets and subsequently artificially contaminated with 10^6 CFU/mL. After 6 d of storage at 4 ºC, a reduction of approximately 87 % in the bacterial count was observed in both samples, compared to the control group of 3.5 log CFU/mL[60].

On the other hand, phages have shown significant efficacy against *E. coli* at critical stages of food processing. In a recent investigation, a T4 phage solution with a titer of 10^9 PFU/mL, immobilized on a chemically modified polycaprolactone film, reduced the bacterial count by 2.4 log units compared to the untreated film (~7 log CFU/g). This was observed in raw beef samples experimentally inoculated with 10^7 CFU/ml *E. coli* O157:H7 after 120 h of challenge at room temperature. These results demonstrate the potential of phages to improve food safety during food packaging[61]. Similarly, an inoculum of 10^4 CFU of a mixture of 6 strains of *E. coli* O157:H7 (2 of these responsible for food outbreaks) added to stainless steel and ceramic surfaces remained at undetectable levels after 1 hour at 23 ºC after treatment with 10^6 PFU of the phage cocktail BEC8, thus proving its efficacy at above ambient temperatures in materials typically used in food processing[62].

Campylobacter jejuni

It is a Gram-negative bacterium of the family Campylobacteraceae[13] that can be found in various birds such as chickens, turkeys, and wild birds, as well as in pets and rodents[8]. It is the most common foodborne zoonotic pathogen worldwide[73], *C. jejuni* causing ~89 % of

infections, followed by *C. coli* (~10 %), *C. fetus*, *C. upsaliensis*, and *C. lari* (~1 %)[2]. Consumption of as few as ~400-500 cells of the pathogen can cause enteritis in humans[74], which manifests with symptoms such as abdominal, head, and muscle pain, bloody watery diarrhea, nausea, and fever, seven to ten days after consumption[8,9]. In severe cases, it can lead to complications such as reactive arthritis, inflammatory bowel disease, and Guillain-Barré syndrome (42 % of cases of this syndrome are associated with *C. jejuni* infection), with children, the elderly, and immunocompromised persons being the most susceptible[75].

The World Health Organization has highlighted *Campylobacter* as a priority pathogen on the global attention list due to its global impact, with a prevalence of 20 to 80 % in several countries in Europe, America, and Asia[75]. In 2010, 95 million cases of campylobacteriosis were reported worldwide, resulting in approximately 21,000 deaths[9]. In addition, EFSA reports that, since 2005, it remains the most prevalent bacterial pathogen in human gastrointestinal infections in the European Union, with an average of 200,000 cases per year and an economic loss of 2.4 billion euros[73,75].

Sources of infection include poor hygiene practices and consumption of contaminated water and unpasteurized milk[13]. However, the main source of transmission is improper handling and consumption of raw or undercooked chicken meat[2]. Despite the limited number of reports and commercial preparations of phages for the biological control of *Campylobacter* in food, in 2023, a review highlights some research demonstrating their efficacy in ensuring food safety[2].

The application of specific phages to reduce *Campylobacter* spp. contamination of feed has focused mainly on broilers. For example, one study showed that treatment with 10^7 PFU of the φ phage reduced the bacterial count of *C. jejuni* by approximately 2 log units, compared to the control group of 4.1 $\log_{10}$ CFU/ml, for five consecutive days in chicken skin samples stored at -20 ºC[76]. Similarly, samples of this type that were experimentally contaminated with 10^4 CFU/cm^2 of *C. jejuni* and stored at refrigerated temperatures showed a bacterial reduction of approximately 2 log units when treated with a solution composted of two phages with a titer of 10^7 PFU/mL[29], and of 0.73 $\log_{10}$ when a single phage with a titer of 10^6 PFU/mL was administered and the samples were maintained under anaerobic conditions[77].

Moreover, the efficacy of phages to combat *C. jejuni* contamination in lamb and beef has shown promising results. In 2020, a group of researchers evaluated the use of 10^6 PFU/mL of phage CJ01 sprayed on pieces of lamb and chicken meat (20 g each) that had been artificially contaminated with 10^4 CFU/mL of a multidrug-resistant strain of *C. jejuni* and stored at 4°C. After 48 h, both samples showed a decrease of ~1.7 $\log_{10}$ CFU/g in the bacterial count, compared to the control group, which had a bacterial count of approximately 4 $\log_{10}$ CFU/g[78]. This reinforces the evidence for the use of phages as biocontrol agents. Likewise, in raw and cooked beef samples experimentally inoculated with 10^4 CFU/ml of *C. jejuni* and

treated with an MOI of 10,000 of phage Cj6, bacterial counts decreased to undetectable levels when stored for 8 d at a temperature of 4 ºC[27].

Commercialized phage products

The production and sale of phage products represents significant progress in microbiology, biotechnology and health[79]. Products in the market are based on a single phage or multiple phages (cocktails); in addition, they must be effective against the largest number of bacterial strains and be strictly characterized to ensure their unique lytic property, eliminating the possibility of transferring toxins, antibiotic resistance genes, and virulence factors[80]. Since the approval of ListShield™, the first phage product approved as GRAS (generally recognized as safe) in 2006[1], multiple FDA-certified phage preparations have emerged worldwide to combat pathogens linked to meat products and their derivatives, whether ready-to-eat or not[81].

The regulation of phage products used as biocontrol agents is based on the acquisition of GRAS status granted by the FDA. To comply with market regulations, it is essential that the level of endotoxins in these products be below 250,000 EU/mL. In addition, GRAS certification establishes a limit of use, allowing only 10^8 PFU per gram of feed[82].

A comprehensive review shows that, until 2021, 53 % (n= 65) of the phage products marketed worldwide have a human therapeutic purpose, 31 % (n= 38) for animal use, 11 % (n= 14) for biocontrol in food, and 5 % (n= 6) for use in the agricultural sector[83].

Phage products used for the biocontrol of pathogens in food have been approved for marketing by health agencies in Canada, Israel, the United States of America, China, Switzerland, and the United Kingdom. All these marketed products primarily combat *Salmonella* (29%; n= 4), followed by *E. coli* (21 %; n= 3) and *L. monocytogenes* (21 %; n= 3), multiple bacteria (14 %; n= 2), and finally *Campylobacter* (7 %; n= 1) and *Shigella* (7 %; n= 1). 78.5 % (n= 11) of the products have received FDA approval[83]. Table 4 presents information on different commercialized phage products used to combat pathogens linked to food of animal origin.

Conclusions

The application of phages in the food industry offers multiple benefits compared to physical and chemical methods, since they alter neither the quality nor the organoleptic properties of food products. In the food sector, phages have demonstrated a considerable decrease in contamination levels, which facilitates biosanitization of surfaces and equipment used in food production, biocontrol in food products (raw, cooked and ready-to-eat), and biopreservation to extend the shelf life of products and minimize risks to consumers. Regulation of phage products is essential to ensure both their quality and efficacy; this oversight is essential to protect public health by mitigating potential health risks and increases consumer confidence. It is crucial to note that, although the use of phages seems encouraging, it must be part of a comprehensive approach that also incorporates good hygiene and management practices.

Table 1: Studies on the use of bacteriophages against *Salmonella*

Bacteriophage	**Bacterium**	**Matrix (contamination dose)**	**Phage application dose**	**Bacteria reduction**	**Source**
LPSEYT (environmental bacteriophage)	*S. enterica*	Pasteurized milk (3 log_{10} CFU/mL).	7 log_{10} PFU/mL	2.19 and 4.22 log_{10} CFU/mL at 4 and 25 ºC, respectively.	[24]
SE07		Beef and chicken slices (10^5 CFU/mL).	10^{12} PFU/ mL	After 12 hours at 4 ºC, ~2 log_{10} CFU/mL	[25]
Felix-01 variant	*S.* Typhimurium	Chicken sausages (300 CFU/ml). After 4 d of storage, 8.2 x 10^6 CFU/mL was recorded.	5.25 x 10^6 PFU/mL.	2.1 logarithmic units after 24 h at 22 ºC.	[26]
P7		Raw beef (10^4 CFU/cm^2).	MOI of 10,000	>5.9 log10/cm^2 in samples stored at 24 ºC for 8 d.	[27]
SJ2	*S.* Enteritidis	Pasteurized raw milk (10^4 CFU/mL). Subsequently, Cheddar cheese was manufactured, from which the samples were obtained.	10^8 PFU /mL.	Complete elimination in cheese made with pasteurized milk; and 50 CFU/g in cheese made with raw milk.	[28]
12 phage		Chicken skin (10^3 CFU/cm^2).	MOI of 100,000.	Complete elimination after 48 h of storage at 4 ºC.	[29]
PA13076; PC2184 (cocktail)		Chicken breast; pasteurized milk (4 x 10^5 CFU/mL).	4 x 10^9 PFU/mL.	2.5 log_{10} CFU in chicken breast samples; and complete elimination in pasteurized milk samples.	[30]
wksl3		Chicken skin (3.25 CFU/cm^2).	2.2 x 108 PFU/mL.	2.43 CFU/cm^2 after storage for 7 d at 8 ºC.	[31]
PHISE (cocktail)		Chicken skin (10^5 CFU/cm^2).	10^9 PFU/mL	After immersion for 30 min, 1 log_{10} CFU/cm^2	[32]

Cocktail composed of 5 phages		Beef, turkey, and chicken (10^5 CFU/mL).	10^9 PFU/mL.	After storage for 10 d at 5 ºC, a reduction of 3.54, 2.84 and 1.67 log units was observed in beef, turkey and chicken samples, respectively.	[33]
SalmoFresh™ in combination with Laryl Arginate (LAE)	*S.* Typhimurium*;* *S.* Heidelberg*;* *S.* Enteritidis	Chicken skin (3 $\log_{10}$ CFU/cm^2).	Application of LAE (400 ppm) followed by 10^9 PFU/mL of the phage product.	2.2-2.5 $\log_{10}$ CFU/cm^2 with 1 day of storage at 4 ºC.	[34]
SalmoFresh™		Modified Atmosphere Packaging (MAP) chicken breast fillets (~3 $\log_{10}$ CFU/g of pathogen mixture)	10^9 PFU/mL.	After storage for 7 d at 4 ºC, 1.2 log10 CFU/g was recorded when MAP+phage product was used; and 0.4 $\log_{10}$ when MAP alone (95% CO_2/5% O_2) was used.	[35]

MOI= multiplicity of infection; PFU= plaque-forming units; CFU= colony-forming units.

Table 2: Studies on the use of bacteriophages against *L. monocytogenes*

Bacteriophage	Bacterium	Matrix (contamination dose)	Phage application dose	Bacteria reduction	Source
Listex™ P100	Mixed strains of *L. monocytogenes* (ScottA, 1/2a, 1/2b, 4b, DSA25).	Slices of cured ham and stainless steel (2-3 logarithmic units/cm^2)	8 log_{10} PFU/cm^2.	Complete removal in both matrices. The ham slices were stored at 4 ºC for 14 d.	[48]
	L. monocytogenes	Turkey and roast beef (10^3 CFU/cm^2).	10^7 PFU/cm^2.	With 28 d storage at 4 ºC, ~2 log units.	[49]
	Mixed strains of *L. monocytogenes* (V7, Bug600, F4393, F5069, ATCC 43257)	Fresh cheese (3.5 CFU/cm^2).	10^8 PFU/cm^2.	In combination with potassium lactate (2.8 %) and sodium diacetate (0.2 %), a reduction of ~3 logarithmic units were maintained for 28 d at 4 °C.	[50]
	L. monocytogenes	Munster cheese (2 x 10^1 CFU/mL).	1.5 x 10^8 PFU/mL y 3 x 10^9 PFU/mL.	After 21 d at 4 ºC storage, reduction of 2-3 log units/cm^2 with the low dose and complete elimination with the high dose.	[51]
		Cured ham (10^3-10^5 CFU/cm^2).	10^9 PFU/cm^2	Complete elimination after 24 h at 4 and 12 ºC.	[41]
ListShield™	*L. monocytogenes* (1/2a, 1/2b, 4b).	Cheese (10^4 CFU/g); smoked salmon (10^3 CFU/g).	10^8 PFU/g (cheese); 9 x 105 PFU/g (smoked salmon).	82 % (0.7 log) in cheese; 90 % (1.2 log) in smoked salmon.	[52]
A511	*L. monocytogenes*	Ready-to-eat chicken breast rolls (10^2 CFU/cm^2).	1.5 x 10^6 PFU/cm^2.	Complete elimination. Storage was for 18 d at 5 ºC.	[53]

	L. monocytogenes (ScottA)	Camembert cheese (1 x 10^3 CFU/cm^2); Limburger cheese (1 x 10 CFU/cm^2).	3 x 10^8 PFU/cm^2.	Stored for 1 hour at 12-13 ºC, Camembert cheese recorded a decrease of 2.5 log units; and a complete elimination in Limburger cheese.	[54]
LMP1 y LMP7	*L. monocytogenes* ATCC 7644	Raw milk (5 x 10^5 CFU/mL).	MOI of 100	2-3 and 1.5 log bacterial units at 4 and 10 ºC, respectively, after 18 d of storage.	[55]

MOI= multiplicity of infection; PFU= plaque-forming units; CFU= colony-forming units.

Table 3: Studies on the use of bacteriophages against *E. coli*

Bacteriophage	Bacterium	Matrix (contamination dose)	Phage application dose	Bacteria reduction	Source
AZO145A	*E. coli* O145:H25	Stainless steel (2.5 cm x 7.6 cm x 0.08 cm coupons) (4.7-5.8 logarithmic units/coupon).	2 x 10^{10} PFU/mL.	2.9 and 1.9 log CFU units at 24 and 48-72 h, respectively.	[63]
e11/2; e4/1c; pp01 (cocktail)	*E. coli* O157:H7	Beef (100 µL of 10^3 CFU/mL).	2 x 10^8 PFU/mL of the phage mixture.	In 80 % of the samples (7/9) bacterial elimination was complete; and 20 % (2/9) had a bacterial count of less than 10 CFU/mL.	[64]
FAHEc1		Raw and cooked beef (<100-10^4 CFU/mL)	8 $\log_{10}$ PFU/cm^2.	~4 $\log_{10}$ CFU/cm^2 After 24 h of storage at 5 and 24 ºC.	[65]
Eco M-AG2, Eco M-AG3, Eco M-AG10 (cocktail immobilized on a cellulose membrane).		Raw beef (10^3 CFU/mL).	10^9 PFU/mL.	Under aerobic conditions at 4 ºC, the bacterial load was maintained at undetectable levels at d 12 to 15 post-treatment.	[47]
EC6; EC9; EC11 (cocktail).	*E. coli* ATCC 25922; O127:H6; O5:H-	Ultra-high temperature pasteurized (UHT) cow's milk; and raw milk (10^5 CFU/mL in both samples).	1 x 10^9 PFU/mL.	At 5 and 25 ºC for 7 d and 1 day, elimination was complete. In raw milk inoculated with O5:H-, regrowth was recorded 6 d (5 ºC) and 9 h (25 ºC) after treatment.	[66]
BL EPEC	Enteropathogenic *E. coli*	Milk (10^6 CFU/mL).	MOI de 0.01	98 and 99 % reduction when samples were stored at room temperature for 24 and 4 ºC, respectively.	[67]

MS1	*E. coli* O26, O45, O103, O111, O121, O145, O157:H7.	Ground beef (2.2 x 10^6 CFU/g).	10^8 PFU/mL.	96.2 - 99.9 % reduction.	[68]
DT1-DT6 (cocktail)	*E. coli* O157:H7	Milk and beef (~10^9 CFU/mL).	~10^9 CFU/mL.	Undetectable levels in milk at 24 h at 4 ºC; 3.0-3.8 $\log_{10}$ CFU/mL in meat at 24 h at 37 ºC.	[69]
T1, T4, T5, O1	*E. coli* O157	Raw beef (10^4 CFU/cm^2).	MOI de 1,000	~ 1.3 log CFU/cm^2	[70]
phT4A	*E. coli* ATCC 13706, ATCC 25922.	Plastic and stainless-steel surface (10^9 CFU/mL).	10^9 PFU/mL.	5.5 and 4.0 CFU/cm^2 on plastic and stainless steel, respectively 12 h post-treatment, prevented 3.2 log CFU/cm^2.	[71]
Cocktail of 21 specific phages	*E. coli* O157, O26, O45, O103, O111, O121, 0145.	Stainless steel surface (7 log CFU/mL); polyethylene coupons (9 log CFU/mL).	9 log PFU/mL.	4.0 log CFU/cm^2 in stainless steel; 4.8 log CFU/cm^2 in polyethylene.	[72]

MOI= multiplicity of infection; PFU= plaque-forming units; CFU= colony-forming units.

Table 4: Phage products marketed against food-borne pathogens

Target bacterium	Company	Product	Approval	COMMERCIALIZ	Applications
E. coli	Intralytix (USA)	EcoShield PX™	FDA	Canada; Israel; USA	O157:H7 before the food is packaged.
	Micreos (NED)	PhageGuard E™		USA	O157 in bovine carcasses.
	FINK TEC GmbH (GER)	Secure Shield E1			Beef and turkey products.
Salmonella	Intralytix (USA)	SalmoFresh™		Canada; Israel; USA	Food additive for poultry, fish, seafood, fruits, and vegetables.
	Micreos (NED)	PhageGuard S™		Canada; Israel	Poultry products.
	Arm and Hammer Animal & Food Production (USA)	Finalyse™ SAL		USA	
L. monocytogenes	Intralytix (USA)	ListShield™	FDA	USA Canada; Israel; Switzerland	Beef products; poultry, fish, and seafood feed additive.
		Listex™	FDA		
	Micreos (NED)	PhageGuard Listex™			Meat products.
Campylobacter	Intralytix (USA)	Compyshield™		USA	Raw red meat products.
Shigella	Intralytix (USA)	ShigaShield™			Meat and vegetable products.
Variety of bacteria	Brimrose Technology Corporation (USA)	EnkoPhagum	Approved	United Kingdom	Removal of *Salmonella*, *Shigella*, *E. coli*, and *Staphylococcus* in meat products.

COMMERCIALIZ= commercialization.

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