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Entry

# Bacteriocins and Bacteriophages as Dual Biological Players for Food Safety Applications

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**Definition:** The development of new techniques for the control of pathogenic microorganisms during food production and for the prevention of spoilage are needed to reduce or replace chemical preservatives. This is due to the trend that consumers are increasingly questioning the use of chemical preservatives because of the many health concerns. Because of this issue, bacteriocins and bacteriophages are increasingly viewed as safe natural preservatives with a long history of various applications during food production and preservation. This minireview considers applications of these two antimicrobials, highlights their mode of action, lists their advantages and, when necessary, their limitations. It also reports recent advances in the use of bacteriophages and bacteriocins either alone or in combination in different food matrices. The incentives and effectiveness offered by these antimicrobials in the field of biopreservation are considered for future applications during food production and preservation.

**Keywords:** bacteriocins; phages; foodborne pathogens; biopreservation



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## 1. Introduction

Foodborne pathogens are responsible for many diseases worldwide. Their presence and persistence in the production environment of the food industry are most often associated with inappropriate disinfection procedures or failure to follow hygiene regulations, making them potentially problematic in this sector [1]. Despite the effectiveness of chemical and physical cleaning techniques, bacteria can evade adverse conditions and persist due to their ability to organize themselves into a multispecies biofilm. This structure is mainly composed of bacterial polymeric extracellular matrix, exopolysaccharides (EPS) and DNA, which enables multispecies bacterial biofilms to withstand harsh conditions. In addition, physical and chemical treatments are not always effective in eliminating biofilms, resulting in potential contamination and alteration of food products, compromising food health and safety [2].

There is growing consumer concern about the adverse effects of treating food with potentially harmful chemicals. This ever-increasing trend has led to a heightened awareness of foods prepared and served with natural ingredients [3]. In this light, bacteriophages, which are bacteria-infecting viruses, and bacteriocins, which are ribosomally produced antimicrobial peptides, could serve as a means to reduce foodborne and spoilage bacteria, as a potential alternative to chemical additives [4,5]. This brief review describes what bacteriocins and phages are and then focuses on their potential applications in the food production and preservation sector.

## 2. Bacteriocins

Briefly, bacteriocins are synthesized by both Gram-positive and Gram-negative bacteria as well as members of the Archaea [6]. In the group of Gram-positive bacteria, the most well-studied bacteriocins are produced by lactic acid bacteria (LAB), with Generally Recognized As Safe (GRAS) status. The first model of a protease-sensitive LAB-bacteriocin was attributed to *Lactococcus lactis* formerly described as *Streptococcus lactis* [7]. These bacteriocins are extracellular antimicrobial peptides ribosomally synthesized, released in their synthesized state or after post-translational modification, which may have a phylogenetically narrow spectrum of bactericidal activity and against which this bacterium possesses a number of specific protective mechanisms [8]. In addition to producing lactic acid as the main end product of sugar fermentation, LAB produces different bacteriocins. These antimicrobial peptides display different characteristics in terms of molecular weight, biochemical properties, spectrum of activity and mode of action [9]. The LAB-bacteriocins were also reported to be noncytotoxic, pH stable and do not affect the gut microbiota because of their sensitivity to the host digestive proteases [10]. LAB-bacteriocins were first categorized by Klaenhammer [11] and then, in different successive classifications, such as those proposed by other investigators [9,12–15]. Recently, a simplified classification has been suggested by Soltani et al. [16] that includes bacteriocins from both Gram-negative bacteria and Gram-positive bacteria in two main categories. These are class I (modified bacteriocins) and class II (unmodified). Briefly, class I contains small, low molecular weight peptides < 5 kDa, that undergo post-transcriptional modifications, whereas class II bacteriocins comprise unmodified peptides with molecular weights ranging from 6 to 10 kDa. Of note, class I is divided into several subclasses, including lanthipeptides, sactipeptides, circular peptides and lasso peptides from Gram-positive and Gram-negative bacteria. Class II bacteriocins include pediocin-like bacteriocins with a YGNGV consensus sequence and unmodified non pediocin-like bacteriocins [16].

In recent years, LAB-bacteriocins have become of increased interest because of their GRAS status [17] and because of their use as biopreservative agents of choice in the food industry to replace chemical agents [18]. Except in some cases of Gram-negative bacteria inhibition [19–23], LAB-bacteriocins are most often active against Gram-positive target strains, which are phylogenetically related to the producing strains [8]. In fact, the absence of activity across Gram-negative bacteria could be explained by the outer membrane, which impedes their access to the inner membrane, where they exert their activity [24]. This argument is no longer valid as some LAB-bacteriocins, as referenced previously, display inhibitory activities towards Gram-negative bacteria through mechanisms that remain to be elucidated [25].

## 3. Bacteriocins in the Food Industry

According to Lahiri et al. [26] bacteriocins should fulfill several criteria, and as such, have to (i) be safe for the human consumption and not negatively impact human gut microbiota, (ii) possess a broad spectrum of antimicrobial activity against foodborne pathogens, (iii) include industrial features like resistance to enzymes in the food matrix, (iv) have stability at elevated temperatures in a wide range of pH values and (v) various salt concentrations [26]. Despite the number of reports on bacteriocins' ability to be introduced in the food sector as biopreservative agents, only nisin and, to a lesser extent, pediocin PA-1/AcH have been authorized as commercial biopreservative agents. Of note, sakacin, plantaricin and carnosine have been proposed as new bioprotective bacteriocins and their development was undertaken to disrupt biofilms [27].

The use of bacteriocins in the food industry is relevant, given their capability to inhibit a wide range of foodborne pathogens and spoilage microorganisms [28]. Because of this attribute, the use of LAB or their metabolites has become increasingly common [29]. Besides their inhibitory properties, which help to expand the food products shelf life, bacteriocins present added properties, such as their inability to positively affect the organoleptic and nutritional value of these food products [30–33]. Therefore, applications of LAB-bacteriocins

can significantly reduce the use of chemicals and respond to the consumer expectations, who are steadily disclaiming the use of chemical food preservatives. LAB-bacteriocins can have a broad or narrow spectrum of activity, enabling them in certain cases to specifically target harmful bacteria, such as *Listeria monocytogenes* [33]. Of note, biofilm formation is a major concern in the food industry, and both pathogenic and spoilage microorganisms can adopt this mode of life, which can compromise disinfection procedures. This contributes to their persistence in the environment and presence on equipment used in the food processing facilities, leading to recurrent cross-contamination of various food products [34]. This results in a threat to the global hygienic value of many food products. LAB-bacteriocins display a potential to disrupt biofilm formation by undesirable pathogenic or spoilage bacteria, such as *Salmonella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *L. monocytogenes* and *Bacillus cereus* [27,35,36]. The adsorption of bacteriocins could be used as a preventive biological means to interfere with bacterial adhesion on abiotic supports and subsequently disrupt biofilm formation. Consequently, bacteriocins associated with other substances offer further advantages and could be the next approach in the agri-food industry to prevent biofilm formation [36].

Bacteriocins in the food industry can be applied in various systems. In fact, bacteriocinogenic strains (bacteriocin producers) could be applied directly in foods, allowing for in situ production and effectiveness in reducing foodborne pathogens, such as *L. monocytogenes*. This approach has been proven during different investigations [37,38]. Furthermore, processes also consist of using purified or semi-purified bacteriocins. Perhaps as a more cost-effective process, bacteriocins can be simply applied as a concentrate resulting from the fermentation of a food substrate, and finally, they may be encapsulated, which enhances their stability and efficacy during processing and preservation [22,39–42]. Bacteriocins can also be used in “smart” packaging to control foodborne pathogens and increase the shelf life of a food product [43,44].

Bacteriocins are clearly suitable for food applications. These small antimicrobial peptides (AMPs) are naturally produced by a number of LAB from fermented foods [45,46]. Related to that, multiple assays of bacteriocin applications have been reported in the literature and presented in Table 1, proving the effectiveness of these natural molecules as effective alternatives to chemically conserved food products.

Importantly, to prevent bacterial resistance to bacteriocins, it should be noted that combinations of bacteriocins with other antimicrobials could lead to synergistic interactions and reduce the phenomenon of resistance. In this light, bacteriocins have been successfully tested with chemical preservatives [31], inulin [47], natural phenolic compounds and essential oils [48,49]. Because of their distinct mode of action, these combinations, as above stated, reduce or prevent the development of resistant bacterial strains. Moreover, bacteriocins have been reported to support various applications when tested collectively with physical treatments [41], such as high pressure [50] or pulsed electric fields [51]. Finally, the combination of bacteriocins with bacteriophages to combat foodborne pathogens continues to result in the design of promising prospective interventions to reduce foodborne bacterial disease and inhibit food spoilage [4,52,53].

In summary, the use of bacteriocins in the food sector offers a number of useful advantages. These antibacterial products are nontoxic and easily metabolized by digestive enzymes [16,33]. Their global use will represent a breakthrough in the food sector, as they are expected to reduce both the use of chemical products and the intensity of the current heat treatment procedures [27,33]. This approach will also be very useful in creating environmentally and economically friendly products that meet consumer expectations.

**Table 1.** Examples of bacteriocins and their targets to be used as biopreservative agents in the food sector.

Producing Strain	Bacteriocin	Application	Target Microorganism	Reference
<i>Pediococcus acidilactici</i> PAC1.0	Pediocin PA-1/AcH	Raw chicken	<i>Listeria monocytogenes</i>	[54]
<i>Latilactobacillus sakei</i> Lb674	Sakacin P	Chicken	<i>Listeria monocytogenes</i>	[55]
<i>Enterococcus faecium</i> CTC492	Enterocins A and B	Ham	<i>Listeria monocytogenes</i> , <i>Lactobacillus sakei</i>	[56]
<i>Enterococcus faecium</i> L50	Enterocin L50A/L50B	Beers	<i>Lactobacillus brevis</i> , <i>Pediococcus dammosus</i>	[57]
<i>Enterococcus faecium</i> FL31	Bacteriocin BacFL31	Ground turkey meet	<i>Listeria monocytogenes</i> , <i>Salmonella</i> Typhimurium	[58]
<i>Lactococcus lactis</i> CSK3533	Nisin/Lacticin	Cheese	<i>Listeria monocytogenes</i>	[59]
<i>Lactiplantibacillus plantarum</i> LMG P-26358	3147/Plantaricin			
<i>Lactocaseibacillus rhamnosus</i> RC20975	Bacteriocin RC20975	Apple juice	<i>Alicyclobacillus acidoterrestris</i>	[60]
<i>Lactiplantibacillus plantarum</i> BM-1	Plantaricin BM-1	Fresh pork meat	<i>Listeria monocytogenes</i>	[61]
<i>Lactobacillus crustorum</i> MN047	Bacteriocin BM1300	Beef meat	<i>Staphylococcus aureus</i>	[62]
<i>Lactiplantibacillus plantarum</i> S7-10	Plantaricin E and F	Honeybee	<i>Escherichia coli</i>	[63]
<i>Lactococcus lactis</i> CAU2013		Fresh cheese	<i>Paenibacillus larvae</i>	[38]
<i>Lactococcus lactis</i> F01	bacteriocin peptide C4B	Fish sausage	<i>Listeria monocytogenes</i> , <i>Clostridium</i> sp., <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Salmonella</i> Typhimurium, <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i>	[64]
<i>Lactiplantibacillus plantarum</i>		Table grapes	<i>Pseudomonas syringae</i> pv. <i>syringae</i> and <i>Botrytis cinerea</i>	[65]
<i>Limosilactobacillus panis</i> C-M2	Lactocin C-M2	Fish	<i>Staphylococcus aureus</i>	[66]
<i>Enterococcus faecalis</i> L2B21K3 and L3A21K6		Ripened cheese	<i>Listeria monocytogenes</i>	[67]

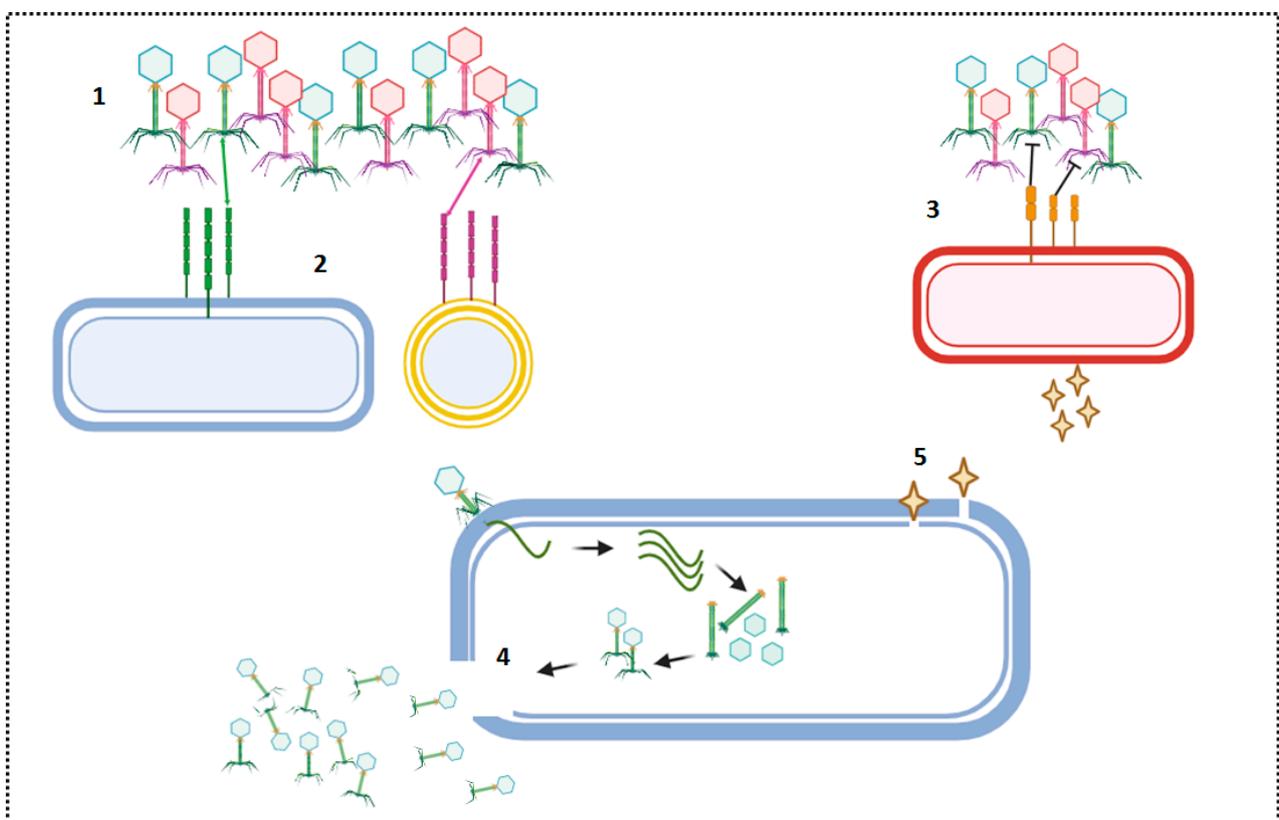
#### 4. Bacteriophages

Historically, bacteriophages were discovered at the beginning of the 20th century by Frederick Twort and Félix d’Herelle, and they were proposed for use as antibacterial agents [68]. The discovery and development of antibiotics (ATBs) in the following decades was the main reason for the decline in the use of bacteriophages to treat bacterial infections in Western countries [69]. In addition, there have been failures and certain factors that have exacerbated the significant decline in bacteriophage research, including (i) the lack of understanding of the heterogeneity and ecology of phages and bacteria; (ii) the risk of selecting highly virulent phages against the patient’s target bacteria; (iii) the use of single phage preparations to treat infections involving mixtures of different bacteria; (iv) the emergence of bacterial host mutants that may be resistant to bacteriophages; and (v) the lack of appropriate characterization or titration of phage preparations; (vi) the lack of gastric pH neutralization prior to oral administration; (vii) the inactivation of phages by the host immune response; (viii) the presence of endotoxins in the phage preparation, and (ix) the lack of a reliability interlaboratory identification of the pathogens responsible for infections [70]. The phenomenon of resistance to ATBs and their global spread is now generating renewed interest in the search for innovative strategies to alleviate this problem. More attention is now being paid to bacteriophages for clinical applications in human and veterinary medicine and in food production [71–73].

Phages are ubiquitous and play an important role in a wide range of biological processes. They are considered to be the most abundant microorganisms on the planet, with an estimated number of  $10^{31}$  in the biosphere [74]. The vast majority of known phages are tailed bacteriophages with double-stranded DNA [75,76]. Unlike traditional ATBs, bacteriophages are highly species-specific, which allows them to potentially maintain an intact microbiota and be adapted for use in food products where they do not alter organoleptic properties or the texture of foods [72,77]. Further advantages attributed to bacteriophages include (i) the low likelihood of inducing comparative antibiotic resistance; and (ii) the potent antibiofilm activity of bacteriophages [78].

The interaction between a bacteriophage and the bacterial host drives the bactericidal activity of bacteriophages. This results in the development of a lytic cycle during which

the bacteriophage genome replicates, followed by transcription and translation, resulting in capsid formation. After assembly, the host cell is lysed by the lytic enzymes called endolysins, in combination with the holins encoded by the phage genome, and the newly formed bacteriophages are released into the environment [79]. Globally, the lytic cycle of bacteriophages consists of an adsorption step (Figure 1), resulting in an irreversible adhesion to the bacterial cell surface involving interactions between the phage attachment proteins and their specific bacterial cell-surface receptors. The receptors are found in the outer membrane, such as LPS for Gram-negative bacteria or teichoic acid and lipoteichoic acid for Gram-positive bacteria on the bacterial cell wall. Efficient recognition of specific phage receptors leads to attachment of the virus and injection of genetic material into the host cell. This process is strictly dependent on the environment and its physico-chemical factors, pH, temperature, availability of nutrients or ions, and physiological state of the bacterial cell [80,81].



**Figure 1.** Biopreservation of food by the synergistic effect of an association between bacteriophages and a bacteriocin produced by a bacteriocinogenic bacterium, which can also play the role of starter (1) consortium of phages, (2) adsorption of bacteriophages to foodborne pathogenic bacteria by specific binding to cell receptors, (3) absence of binding between the bacteriophages and the bacteriocin-producing bacteria, (4) inhibition of pathogens by the phage lytic cycle, which ends with cell lysis involving holins and endolysins, (5) plus the antagonistic effect of bacteriocin on the integrity of the cytoplasmic membrane and peptidoglycan. Figure created with [BioRender.com](https://www.biorender.com).

### 5. Bacteriophages in the Food Sector

Bacteriophages are a major cause of milk fermentation failure due to their infection of bacterial starter cultures [82]. However, their use alone or in combination with other antibacterial agents is a promising means to be utilized in the food sector to fight pathogenic and spoilage bacteria [71]. As reported, phages are abundant in the environment. Their presence has been pointed out in unpolluted water at levels of  $2 \times 10^8$  bacteriophages/mL, and they are regularly consumed in foods [69].

Importantly, phages predicted for use as antimicrobials should possess several important characteristics [71]. For example, they should undergo lytic cycles and not lysogenize as prophages. Their host range must cover all epidemiologically relevant strains found in the targeted species. In addition, phages with minimal transduction capacity should be used to avoid phages that could transmit bacterial DNA to subsequent hosts. Next, their stability in the environment of use should be considered important for food applications. There is also the possibility of developing resistance to these biological agents, but this limitation could be mitigated by using phage cocktails rather than a monophagic preparation [71,83]. The Food and Drug Administration (FDA) approved the ListShield™ phage consortium against *L. monocytogenes* as a food additive in 2006. Subsequently, the number of bacteriophage preparations for human consumption that have received GRAS status from the FDA has expanded to include SalmoFresh™ and PhageGuard S™ [84]. The efficacy of new phage preparations has been confirmed by numerous studies that have demonstrated their effectiveness against the most commonly implicated foodborne bacterial pathogens [85]. It should be noted that bacteriophages are also used in animals and in the production of meat such as poultry and fish [70,79], as well as in the development of smart food packaging [86]. Bacteriophages have been successfully used in the treatment and diagnosis of plant diseases and in the biocontrol of phytopathogenic bacteria [87,88]. Phages have also been used in wastewater treatment [89] and are widely used for pathogen control and detection in the dairy industry [90–92].

The lytic effect of phages against *L. monocytogenes* has been reported in several studies [78,91,93–96] as this bacterium is the etiology of listeriosis disease in humans. Phages have a high lethality rate against their bacterial hosts and can be found at any point in the food production process, even during storage, due to the ability of phages to persist at temperatures  $< 0\text{ }^{\circ}\text{C}$  [97]. In this regard, the consortium of LM-103 and LMP-102 phages was found to reduce the load of *L. monocytogenes*, including the serotypes 1/2a, 1/2b and 4b commonly associated with human listeriosis, by 2.0 to 4.6 log units compared to the control on honeydew melons [52]. It is also important to eliminate or reduce the persistence of *L. monocytogenes* in the form of biofilms on various surfaces in the agri-food industry. In this context, bacteriophage P100 solution, when applied at 8 log PFU (plaque forming units)/mL, successfully removed *L. monocytogenes* serotype 1/2a (LM6) biofilms from polystyrene surfaces [98]. Another targeted foodborne bacterial pathogen is *Staphylococcus aureus*, which produces heat-stable enterotoxins, adopts a biofilm lifestyle, can develop antibiotic resistance and can evolve genetic mutations that lead to harmful strains, such as those derived from methicillin-resistant *S. aureus* (MRSA) [99]. In a recent study conducted by Kwak et al. [100], it was reported that the application of bacteriophage KMSP1 at a multiplicity of infection (MOI) of  $10^4$  resulted in a significant reduction of 8.8 log CFU/mL on *S. aureus* viable cells in a pasteurized milk study, compared to 4.3 CFU/cm<sup>2</sup> in the cheddar cheese after 24 h exposure. The presence of phages allows reducing the intensity of physical treatments of the milk, such as high hydrostatic pressure, limiting its negative impact on the typicity and organoleptic quality of the product [101].

Other researchers have reported the beneficial effects of lytic phages on several pathogenic species in various food matrices, such as the inhibition of *Enterobacter cloacae* growth in pasteurized milk and yogurt by vB\_EclM-EP1 and vB\_EclM-EP2 phages [92]. Similarly, two multidrug-resistant strains of *Vibrio parahaemolyticus* and *Vibrio cholerae* isolated from water samples were effectively lysed by two phages, vB\_VpM\_SA3V and vB\_VcM\_SA3V, belonging to the former *Myoviridae* family [102]. Next, Choi et al. demonstrated the inhibitory properties of a polycaprolactone film prepared with T4 bacteriophage against *Escherichia coli* O157:H7 [86]. The efficacy of the bacteriophage AZO145A in inhibiting the formation of *E. coli* (STEC) O145:H25 biofilm was also reported, supporting its use to reduce the biofilm on stainless steel surfaces in the food industry [103]. Other applications of bacteriophages to reduce bacterial pathogens in various food matrices are listed in Table 2.

However, the protein nature of bacteriophages and their endolysins, coupled with their sensitivity to various external factors experienced during food processing, such as temperature, acidity and salinity, are at the root of phage instability in the food environment [104]. Among the solutions proposed is the search for and characterization of thermostable phages and endolysins, such as LysCPS2, active against *Clostridium perfringens*, with optimal conditions of pH 7.5–10 and a temperature of 25–65 °C, but also able to withstand 95 °C for 10 min [105]. Next, bacteriophage encapsulation was shown to be effective and a good alternative [106]. The stability of *Lactococcus* P008 phage protected by capsules of milk proteins provided improved protection at pH 2.0 compared to nonencapsulated bacteriophage [107]. In addition, combining phages with other antibacterial agents can increase their lytic power and overcome certain deficiencies [4,108].

**Table 2.** Examples of bacteriophages that could be used as biopreservative agents.

Bacteriophages	Application	Target Microorganism	Reference
Phage BPECO19	Chicken meat	<i>Escherichia coli</i> O157:H7	[109]
Phage A511	Cooked meat	<i>Listeria monocytogenes</i>	[110]
Phage Akh-2	Aquaculture	<i>Aeromonas hydrophila</i>	[111]
Phages LSA2308 and LSA2366 (alone or as cocktail)	Milk production chain	<i>Staphylococcus aureus</i>	[112]
Phage T156	Milk	<i>Salmonella</i> Typhimurium	[113]
Phages SE-P3, P16, P37 and P47 (alone or as cocktail)	Raw chicken meat	<i>Salmonella enteritidis</i>	[114]
Cocktail phages (C14 s, L1, V9 and LL15)	Fruits and vegetables	<i>Escherichia coli</i> O157:H7	[115]
Phage A511	Cheese	<i>Listeria monocytogenes</i>	[116]
PhageGuard Listex™ P100	Fuet, cocked ham and fresh cheese	<i>Listeria innocua</i>	[117]

## 6. The Combination of Bacteriophage and Bacteriocin: A Tool against Foodborne Pathogens

The above-mentioned examples of applications of bacteriocins and/or bacteriophages in the food industry as biological and natural agents have been demonstrated alone or in combination in various studies recently reviewed by Rendueles et al. [4]. Note that the combination could also be extended to physical techniques. In fact, a three-way combination of a high-pressure treatment with bacteriophage P100 and a bacteriocinogenic strain of *Pediococcus acidilactici* was successfully used to inhibit *L. monocytogenes* in a fermented meat sausage preparation [94]. A synergistic effect with Pediocin PA-1/AcH in milk has also been reported [118]. Combining the same phage with Enterocin AS-48 inhibited the growth of *L. monocytogenes* in fish stored at 4 °C [119]. The importance of this synergy was confirmed in another experiment in which *S. aureus* strain KCTC 3881 was significantly inhibited by the combination of a bacteriocin produced by *L. lactis* CJNU 3001 and the SAP84 phage. This was compared with the effect of each treatment alone [53]. In addition, Heo et al. [120] reported that the combination of the bacteriocinogenic *Streptococcus hyointestinalis* B19 and a cocktail of two bacteriophages (P4 and A3) completely eradicated the strain *C. perfringens* KCTC 3269T [120]. Exploring and developing the potential of these natural antibacterial agents in the food sector certainly offers positive options to ensure that food products are highly protected and meet consumer expectations for naturally preserved foods.

## 7. Conclusions

The aim of this minireview was to support bacteriocins and bacteriophages as natural, effective means of food preservation. It is, therefore, timely and desirable to replace the chemical agents currently in use, which have been vociferously rejected by consumers around the world for their harmful effects on human health. However, regulations need to be harmonized to allow the gradual use of these natural substances, and further studies, particularly toxicological studies, are needed to prove their safety.

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