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Bacteriophages in Food Applications: From Foe to Friend

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Abstract

Bacteriophages (phages) have traditionally been considered troublesome in food fermentations, as they are an important cause of starter-culture failure and trigger significant financial losses. In addition, from an evolutionary perspective, phages have contributed to the pathogenicity of many bacteria through transduction of virulence genes. In contrast, phages have played an important positive role in molecular biology. Moreover, these agents are increasingly being recognized as a potential solution to the detection and biocontrol of various undesirable bacteria, which cause either spoilage of food materials, decreased microbiological safety of foods, or infectious diseases in food animals and crops. The documented successful applications of phages and various phage-derived molecules are discussed in this review, as are many promising new uses that are currently under development.

INTRODUCTION

Bacteriophages (phages) are viruses that infect and often kill bacteria. They pose a persistent threat in the food fermentation industry because of their ability to inhibit the growth of bacterial starter cultures. This problem is especially prevalent in dairy fermentations involving members of lactic acid bacteria (Garneau & Moineau 2011) and is generally associated with virulent phages. Temperate phages, however, are known to contribute to the pathogenicity of certain food-related bacteria, as they encode virulence factors that, through evolution, have transformed otherwise harmless bacteria into dangerous pathogens. Examples include the CTX phages associated with cholera toxin (Boyd et al. 2000) or the Shiga-converting phages associated with hemorrhagic *Escherichia coli* (Krüger & Lucchesi 2015). Temperate phages have also been reported to improve the fitness of a pathogen, for example, via the transduction of antimicrobial resistance genes (Colavecchio et al. 2017).

From a positive perspective, virulent phages can be exploited for the biocontrol of spoilage bacteria, thus reducing food waste, which is a major economic problem globally (EC 2011). Similarly, phages can be used to eliminate dangerous bacterial pathogens from food materials, leading to a promising approach for the reduction of foodborne illnesses, which is another significant global problem, as indicated in **Table 1** (WHO 2015). Both of these phage applications have attracted considerable research interest in recent years.

Phages have been exploited successfully to control bacterial contamination of foodstuffs in research trials, and some phage formulations, including ListShield™ and SalmoFresh™ (both produced by Intralytix Inc.) for the control of *Listeria monocytogenes* and *Salmonella enterica*, respectively, have been awarded Generally Recognized as Safe (GRAS) status for their use in the food industry. A more extensive list of currently available commercial phage products has been recently compiled (de Melo et al. 2018). This review outlines situations in which phages present an economic threat to the fermentation industry, affecting yields and/or safety in fermented products. It also discusses the phage-based solutions to such problems. In addition, it presents a variety of recent developments that further contribute to phage-based biopreservation, biocontrol, and pathogen detection for the food industry.

Table 1 Median global estimates of the disease burdens caused by foodborne bacterial pathogens during the year 2010[a]

Bacterial species	Illnesses	Deaths	Percent Mortality	DALYs
Campylobacter spp.	95,613,970	21,374	0.022	2,141,926
Enterotoxigenic *Escherichia coli*	86,502,735	26,170	0.03	2,084,229
Salmonella enterica	78,707,591	59,153	0.075	4,067,929
Shigella spp.	51,014,050	15,156	0.029	1,237,103
Enteropathogenic *E. coli*	23,797,284	37,077	0.156	2,938,407
Salmonella Typhi	7,570,087	52,472	0.69	3,720,565
Salmonella Paratyphi A	1,741,120	12,069	0.69	855,730
Shiga-toxin-producing *E. coli*	1,176,854	128	0.01	12,953
Vibrio cholera	763,451	24,649	3.23	1,722,312
Brucella spp.	393,239	1,957	0.5	124,884
Mycobacterium bovis	121,268	10,545	8.7	607,775
Listeria monocytogenes	14,169	3,175	22.4	118,340
Total	347,415,818	230,625	NA	19,632,153

[a]Data accumulated from the WHO survey on global foodborne illnesses (WHO 2015).
Abbreviations: DALYs, disability-adjusted life years; NA, not applicable.

PHAGES: DISCOVERY AND MECHANISM OF ACTION

The term bacteriophage was introduced by French-Canadian microbiologist Felix d'Herelle in 1917 upon his isolation of an invisible microbe from the stools of dysentery patients. During the following two decades, several commercially available phage products emerged, although their application for the elimination of infections was often inconsistent owing largely to the lack of phage biology knowledge at the time. The discovery of penicillin in 1928 heralded the beginning of the antibiotic era, and by the 1940s the application of phages as antibacterials had diminished in much of the world (Kuchment 2012). Nevertheless, these applications have continued in regions of the former Soviet Union. Significantly, the emerging multidrug resistance problem in bacterial pathogens has prompted a renewed interest in the exploitation of phages as therapeutic antibacterial agents.

Phages are considered to be the most abundant biological entities on the planet, with estimated particle numbers of more than 10^{31} (Hendrix 2003). They are usually found where their specific bacterial hosts thrive, given that they are obligate intracellular parasites and unable to propagate without a bacterial cell. They are broadly classified as either virulent or temperate.

In the case of virulent phages, following phage attachment and injection of its genome into the host cell, the host DNA replication and protein synthesis machinery is exploited to synthesize new phage particles, which are released from the cell, usually culminating in the death of the bacterium. This is termed the lytic infection cycle. Although temperate phages are capable of replicating in this way, they also have the ability to replicate using the lysogenic cycle in which their DNA can become part of the bacterial genome as a prophage. Induction, or the excision of the prophage from the genome, can occur spontaneously or in response to cellular internal or external triggers (Nanda et al. 2015). This results in lysis and release of progeny phages that may proceed to lyse or lysogenize other susceptible bacteria.

PHAGES: ENEMIES OF THE FERMENTATION INDUSTRY

Phage activity is a major problem in fermentation processes that rely on bacterial starter cultures, particularly dairy fermentations, which, by their nature, utilize vast volumes of liquid substrate for bacterial culture growth, facilitating rapid dissemination of phages throughout the factory. The destructive potential of phages is exaggerated in modern processes that employ cultures on a more or less continuous basis and need vast numbers of bacterial cells to process large volumes of milk to cheese or yogurt. Phage predation of sensitive starter-culture strains can result in the retardation of acidification, causing delays in the process, dairy products with a higher than normal pH and a concomitant inferior quality (with an increased risk of food safety issues), or, in extreme cases, a complete halting of the fermentation schedule. Phages enter dairy fermentation plants in raw milk, where they are present naturally, after which they may be distributed from milk and whey throughout the processing environment, facilitated by aerosolization events (Verreault et al. 2011). The various regimes used to counteract phages include rigorous sanitization, rotation of cultures, use of phage-inhibitory media for culture preparation, and strict asepsis in culture propagation (Coffey & Ross 2002). In industrial practice, when significant levels of lytic phages are detected for a particular strain, the strain is generally replaced by a phage-unrelated strain(s) or a phage-resistant spontaneous mutant. However, such mutants often exhibit slow acid-producing ability and can also revert to phage sensitivity, which limits their usefulness in practice. The economic and technological problems posed by phage infection of lactococcal and other starter cultures have provided a powerful motivation for the study of the mechanisms by which these bacterial strains naturally protect themselves. Phage-resistance systems identified in

various bacterial species, which have been described in the scientific literature, include phage adsorption inhibition, injection-blocking, restriction–modification, abortive-infection, and CRISPR systems (Labrie et al. 2010). Improvement of the phage-resistance properties of defined strains, via conjugal introduction of phage-resistance plasmids encoding phage resistance, has been applied (Sanders et al. 1986). Nevertheless, there are reports of phages mutating and evolving to circumvent these resistance systems. The various efforts to minimize these phage-related difficulties all add to expenses in the industry (Garneau & Moineau 2011).

Temperate phages can also have an impact on fermentations. Many starter-culture bacteria contain prophages, and spontaneous induction of these under manufacturing conditions may cause lysis of the components of the starter cultures, resulting in the same problems as described above (Coffey & Ross 2002). Interestingly, it has been shown that partial lysis of *Lactococcus lactis* starter strains due to prophage induction is possibly beneficial for the development of cheese flavor because of cytoplasmic enzyme release (O'Sullivan et al. 2000), and thus the presence of lysogens in a starter culture may not be an entirely undesirable situation. Prophages might also be responsible for the resistance of a lysogenic strain to further infection by encoding the genes responsible for superinfection immunity and superinfection exclusion (Canchaya et al. 2003).

TEMPERATE PHAGES AND THEIR SHAPING OF FOODBORNE PATHOGENS

While in the prophage state, most of the gene products of temperate phages remain dormant until the phage is induced to enter the lytic cycle. However, some prophages encode gene products that affect the host-cell phenotype. This process is called lysogenic conversion. Among these so-called converting phages, some carry toxin-encoding genes that can enhance the virulence of the bacterial host. These genes, once integrated into the bacterial chromosome, can cause the once harmless bacteria to release disease-causing toxins. There are several examples of such bacteria; and among them are those that are orally ingested by humans in food or water such as Shiga-toxin-producing *E. coli* (STEC) and *Vibrio cholerae*.

Hemolytic uremic syndrome (HUS) is associated with hemorrhagic *E. coli* such as the serogroup O157:H7, which carry the prophage-encoded Shiga toxins (Stxs). These Stx-producing pathotypes are associated with human infections linked to the consumption of contaminated bovine-derived products or ready-to-eat (RTE) foods (CDC 2018). After ingestion of this pathogen, colonization of the epithelium of the large intestine leads initially to hemorrhagic diarrhea and production of Stxs. Once bound to a eukaryotic cell carrying the globotriaosylceramide (Gb3) receptor, the toxin is internalized and transported to the endoplasmic reticulum, where it causes ribosomal inactivation and, eventually, cell death (Obrig 2010). The phages responsible for Stx production are closely related to lambdoid phages and during lysogeny are integrated into the *E. coli* chromosome. A large number of *stx*-carrying phages have been identified to date, which increases the number of possible *E. coli* hosts available for lysogenic conversion (Krüger & Lucchesi 2015). Non-O157 *stx*-carrying *E. coli* strains are frequently reported (Hughes et al. 2006).

Cholera, caused by the Gram-negative *V. cholerae*, is transmitted to humans by the fecal–oral route. Virulent organisms that reach the small intestine may adhere, colonize, and secrete the cholera enterotoxin (CTX). The toxin binds to the plasma membrane of intestinal epithelial cells and releases an enzymatically active subunit that causes an increase in cyclic adenosine monophosphate (cAMP) production. The resulting high intracellular cAMP level causes massive secretion of electrolytes and water into the intestinal lumen, leading to severe and often fatal dehydration. The CTX-converting phage in this case is a filamentous single-stranded DNA phage in which the cholera toxin is encoded by *ctxA* and *ctxB* genes. Although integrated into the bacterial genome,

the CTX prophages are found on each of the two *V. cholerae* chromosomes or arranged in tandem on the larger of the two (Boyd et al. 2000). The genome of CTX phage is 6.9 kb long and consists of two regions. The core region contains the toxin genes as well as proteins that are thought to form the virus coat. The other, so-called RS2 region contains the genes that control the replication, regulation, and integration of the phage (Boyd et al. 2000).

Antimicrobial resistance genes can also be introduced into bacterial genomes by phage transduction, and this has been observed in the case of certain foodborne pathogens. For example, tetracycline and chloramphenicol resistance genes of *Salmonella* Typhimurium DT104 were transduced into the previously sensitive strain DT16 from strain DT17 by the P22-like phage ES18 (Schmieger & Schicklmaier 1999). Phage P1 has also demonstrated its ability to transfer the β-lactamase gene between *E. coli* strains, resulting in multiple antimicrobial resistances (Kenzaka et al. 2007). Dissemination of antibiotic resistance in these important food pathogens has an obvious detrimental impact on human health, as some antibiotic treatments are no longer effective.

ADVANTAGES OF USING PHAGES TO ELIMINATE BACTERIA IN FOODSTUFFS

The application of phages for the elimination of undesirable bacteria in foods has been in practice for several years in certain jurisdictions (Endersen et al. 2014). For phage applications in foods, propagation, purification, and production costs are considerably less expensive than those that are required for phage interventions in humans, as the latter formulations must adhere to more stringent endotoxin limits (Bonilla et al. 2016, Pirnay et al. 2018, Szermer-Olearnik & Boratyński 2015). There are no food safety issues associated with the oral ingestion of phages applied to foods, as phages are naturally present in high numbers in the environment and accordingly exist naturally on many food materials and are thus unwittingly ingested by humans. Regarding biocides, which act on nonspecific sites on bacterial cells, biocide resistance can develop with multiple cell receptors mutated, including some whose alterations have implications for antibiotic resistance (Fraise 2002). With the increased global demand for foods produced without the use of biocides and chemical preservatives, phages offer a natural means of biocontrol. A big advantage is that the virions do not persist for long in the environment without a host (Jones et al. 2012), unlike antibiotics and biocides that can persist in the soil leading to a further risk of bacterial resistances (Tadeo 2008, Thiele-Bruhn 2003). Phages exclusively target bacteria, but more importantly, they generally have specificity within a single genus or species or even a subgroup of bacterial strains within a species. Nontarget bacteria such as the indigenous human flora remain unaffected by the phages that were applied to foods to eliminate a specific pathogen. Phages also have the advantage of the ability to infiltrate bacterial biofilms and infect cells contained within, unlike many antibiotics or biocides that work most effectively on planktonic cells (Harper et al. 2014, Yan et al. 2014).

THE USE OF PHAGES TO ELIMINATE FOOD SPOILAGE BACTERIA AND ANIMAL PATHOGENS

Phages have been exploited both experimentally and in practice to eliminate spoilage organisms in a variety of foodstuffs, thus reducing food loss and the associated commercial costs. Bacterial spoilage of food materials can occur pre- or postharvest or after a product is manufactured. The application of specific phages can either prevent or minimize the damage by such bacteria at any of these stages.

Preharvest Food Spoilage Control in Crops

Not long after phages were discovered, two scientists from Michigan Agricultural College isolated an inhibitory substance from the liquid of decomposed cabbage that prevented the spoilage of cabbage by *Xanthomonas campestris* pv. *campestris* (Mallmann & Hemstreet 1924). Phages have since been used in laboratory and field trials against a number of plant spoilage organisms, with success in many cases, as reviewed recently (Buttimer et al. 2017). In 2015, the manifestation of Pierce's disease caused by *Xylella fastidiosa* was successfully prevented in artificially infected grapevines using a high-titer mix of four lytic phages applied three weeks after pathogen inoculation (Das et al. 2015). Peppers and tomatoes are vulnerable to bacterial infection caused by *Xanthomonas campestris* pv. *vesicatoria* and *Pseudomonas syringae* pv. *tomato*, and in 2005 the Environmental Protection Agency (EPA) approved the use of the commercial phage-based product AgriPhage™ (OmniLytics Inc.) for the control of these pathogens. This product is designed to be used in place of copper-based bactericides, which can build up in the soil and cause copper-based resistances in bacteria (**http://www.agriphage.com**). Phage therapies in an external environment may be ineffective because of harsh environmental conditions and the lack of host prevalence, which cause the phages to fail to propagate and persist in high numbers. An interesting approach to circumvent this problem was devised in the case of apple and pear tree fire blight by *Erwinia amylovora*. Phages and a phage-susceptible apathogenic bacterium, *Pantoea agglomerans*, were cointroduced to artificially infected trees. This provided a means for the continuous propagation of phages to reduce the onset of fire blight (Lehman 2007). Erwiphage PLUS is now available for the control of *E. amylovora* (**http://www.erwiphage.com**). Other crop-spoilage bacteria that have attracted interest in phage research include *Dickeya solani*, *Streptomyces scabies*, and *Ralstonia solanacearum* (Buttimer et al. 2017).

Veterinary Use of Phages in Food Animals

Bacteria posing a health risk to agricultural animals may cause an undesirable change in product quality and can cause losses in yield because of the unsuitability of meat from affected animals for consumption. Phages have been investigated for their suitability to treat infection in food animals, improve animal health, and increase animal growth rates.

Poultry. Avian pathogenic *E. coli* (APEC) strains are the most common cause of colibacillosis, a condition in poultry where the bacteria can invade the extraintestinal cavity, causing reduced egg production, mortality, and carcass rejection (Guabiraba & Schouler 2015). To investigate alternative colibacillosis control methods other than conventional antibiotic therapy, Huff et al. (2002) applied phages to avian air sacs for prevention of APEC infection. They documented an inverse relationship between administrated phage titer and bird mortality. The following year, the authors determined that intramuscular injection of phages was more effective than an air-sac application to treat established *E. coli* infections, probably because of the inability of the localized application to access systemic bacteria (Huff et al. 2003). To overcome the gastric stresses that could inactivate phages during oral administration, chitosan nanoparticles were exploited to protect *E. coli* phage ΦKAZ14. The encapsulated phage treatment resulted in only a 16% mortality rate, in comparison to a 50% mortality using naked phages (Adamu Ahmad et al. 2016).

Also in poultry, *Clostridium perfringens* is the causative agent of necrotic enteritis (NE), a disease that inhibits weight gain and causes increased mortality. Intralytix has marketed a phage product, INT-401TM, aimed at reducing problems associated with *C. perfringens* and thus preventing associated economic losses (Miller et al. 2010).

Cattle. *Staphylococcus aureus* bovine mastitis commonly leads to decreased quality and yield of milk produced from infected cows. As an alternative to traditionally used antibiotics, which may persist as residues in milk, a cocktail of *S. aureus* phages tested in murine models showed promise in reducing bacterial counts and improving the pathology of mastitic mammary glands. The authors of this study also proposed a combined phage–antibiotic application with a much lower dose of antibiotic than would typically be administered (Breyne et al. 2017).

Enteropathogenic *E. coli* (EPEC) is a common cause of potentially fatal diarrhea in newborn calves. With the neutral pH of the calf abomasum (Foster & Smith 2009), phages, which are generally considered to be acid labile, could be a prospective oral treatment for this condition. Indeed, the efficacy of phages to cure EPEC diarrhea was confirmed as far back as 1983, in a landmark study by Smith and Huggins. Interestingly, a phage-resistant EPEC was isolated during the study but proved to be less virulent than the original strain (Smith & Huggins 1983).

Bovine Johne's Disease is associated with *Mycobacterium avium* subsp. *paratuberculosis* (MAP), which evades drug treatments through its residence within macrophages (Hostetter et al. 2003). Although phages cannot penetrate eukaryotic cells, certain strategies can be employed to treat intracellular pathogens using phages. A solution to this problem was demonstrated by Danelishvili et al. (2006), who exploited the avirulent *Mycobacterium smegmatis* (susceptible to the same phage) to transport and release MAP phages into the MAP-infected eukaryotic cell. The efficacy of this approach was also confirmed in murine studies by the same authors (Danelishvili et al. 2006). This approach has been further developed using liposome-enclosed phages to penetrate macrophages and has the advantage of eliminating unnecessary mycobacterial antigen exposure (Nieth et al. 2015).

Brucellosis-associated abortion of calves is another bovine condition that could potentially be prevented with phages. The research is still in its infancy, but phages were shown to bring about reduced splenic colonization by *Brucella abortus* in mice following intraperitoneal injection of phages (Prajapati et al. 2014).

Swine. Antibiotics have been widely used in pig production. This is believed to result in higher levels of antibiotic resistance in bacterial pathogens, thus reducing the efficacy of many antibiotics in human medicine. This problem has resulted in a call for a worldwide ban on unnecessary antibiotic use in agriculture (WHO 2017). It was reported by Zhang et al. (2015) that establishment of intestinal pathogenic *E. coli* or *Salmonella* species in pigs can decrease nutrient digestibility and, thus, growth performance in the animal. Replacing antibiotics with phages with the aim of reducing the levels of these bacteria has been investigated in pigs by several research groups. Orally administering phages specific for diarrhea-causing *Salmonella*, *E. coli*, and *Clostridium* species resulted in an improved feed-conversion ratio in a number of pig studies (Han et al. 2016, Kim et al. 2014, Lee et al. 2016). Overall, the replacement of antibiotics with phages has been reported to have promising effects on animal development and has been shown to reduce the incidence of severe diarrhea in the animals.

Aquaculture. High-density aquaculture is prone to a variety of contagious bacterial infections. On the basis of the assumption that 10^{30} phages reside in global waters (Whitman et al. 1998), it seems sensible to exploit this natural abundance to design phage therapies to treat diseases of farmed aquatic creatures. In 2017, the LIFE13 ENVIPHAGE project confirmed that phage applications do not stimulate the immune system of fish, do not alter the aquatic bacterial ecosystem, and have no impact on human health (**http://www.enviphage.eu**). One of the most common disease-causing agents in fish is *Vibrio harveyi*, and research trials have demonstrated the efficacy of specific phages in preventing and eradicating associated marine diseases. A 25% survival rate

of giant tiger prawn larvae was increased to 80% with the application of phages to control luminous vibriosis in a shrimp hatchery (Vinod et al. 2006). In the case of abalone shellfish, Wang et al. (2017) reported therapeutic applications of *Vibrio* phages, which resulted in a dramatically increased survival rate in these seafood creatures (Wang et al. 2017). Such findings may well be transferrable to the treatment of *V. harveyi* infections in several other aquatic animals.

Other fish diseases that have been successfully treated with phages include those caused by *Flavobacterium* species, *Edwardsiella tarda*, *Lactococcus garviae*, and *Streptococcus iniae* (ChiHsin et al. 2000, Laanto et al. 2015, Matsuoka et al. 2007, Nakai et al. 1999). In addition, Proteon Pharmaceuticals (**http://www.proteonpharma.com**) has developed a phage product, BAFADOR®, that is designed for commercial use in aquaculture to eliminate *Pseudomonas* and *Aeromonas* infections.

Phage-Mediated Biopreservation of Postharvest and Processed Foodstuffs

The prospect of using phages as preservatives to prevent microbial damage of processed foods and thus prolong shelf life has been explored. Liquid foods are good candidates for phage inclusion, as phages can diffuse freely through the medium, increasing the likelihood of physically meeting their target bacterium. Beer, for example, is frequently contaminated by lactic acid bacteria. The contamination of beer by *Lactobacillus brevis* was controlled successfully by a high-titer application of the phage SA-C12 during small-scale lab trials (Deasy et al. 2011). In the case of milk, pasteurization typically eliminates human pathogens, but low levels of spoilage organisms may remain after the pasteurization process, or, if not, their heat-stable enzymes may still be active, causing milk to spoil prematurely even after pasteurization (particularly in the case of *Pseudomonas*). The feasibility of controlling these spoilage bacteria using phages was recently investigated by Hu et al. (2016), who determined that it was possible to reduce *Pseudomonas* growth and spoilage activity in raw milk (Hu et al. 2016).

Raw meats are prone to bacterial spoilage despite refrigeration and protective packaging. Phages were successfully exploited to control *Brochothrix thermosphacta* in pork segments, resulting in a significant delay of spoilage (Greer & Dilts 2002). In the case of seafood spoilage by *Serratia* species, the application of phage AZT6 in mackerel fillets was successful in reducing *Serratia* loads by more than 90% after a 6-day storage period at 6°C. Confirmation of the phage's activity on solid food during refrigeration is important given the lack of metabolic inactivity of the bacterial host at low temperatures. Lysis from without was proposed to have played a role in the bactericidal effect observed (Hernández 2017).

PHAGE-MEDIATED CONTROL OF BACTERIAL PATHOGENS IN FOOD

Many foods can pose a risk to human health due to contamination by a wide variety of bacterial pathogens, which can cause illness and, in extreme cases, death (WHO 2015). A variety of different food materials, including poultry, meats, dairy products, seafood, and vegetables, are prone to contamination by a wide range of important pathogens. Many of these foods are produced in intense farming systems using industrial-scale processing, further increasing the risk of contamination. In recent years, phages have been shown to be widely applicable for improving safety in a wide range of food materials.

Campylobacter species

Campylobacter infection is the most common cause of bacterial foodborne illness globally (WHO 2015), and poultry is considered to be the most important source. During poultry slaughter, the

intestinal contents (the primary reservoir of *Campylobacter*) frequently contaminate the external carcass with this pathogen (Blaser et al. 1980).

Campylobacter phages have been investigated for their usefulness as antibacterial agents over the past 15 years, beginning with the work of Goode et al. (2003), who focused on the control of *Campylobacter jejuni* in meat applications. These authors reported a 95% reduction in *C. jejuni* contamination on poultry meat following high-titer phage applications (Goode et al. 2003). Oral administration of phages to live broilers with the aim of reducing intestinal *Campylobacter* has also been explored by a number of research groups. In one study, *Campylobacter* levels were successfully reduced in broilers when phages were applied in both drinking water and solid feed (Carvalho et al. 2010). In other studies, orally administered phages also resulted in reduction but not complete elimination of *Campylobacter* in the intestine. Maximum reductions tended to be seen around one to three days post-administration (Hammerl et al. 2014, Wagenaar et al. 2005).

An obvious limitation of oral administration of phages is that only low levels of the agent actually reach the intestinal reservoir of *Campylobacter* because of damage by gastric acid. Accordingly, in a number of oral phage trials, $CaCO_3$ was coadministered with the *Campylobacter* phages as an antacid protectant to increase the number of viable phages that reach the intestinal reservoir of the target pathogen (El-Shibiny et al. 2009, Fischer et al. 2013, Loc Carrillo et al. 2005). Encapsulation is another promising approach for protecting phages from low pH, as demonstrated in a recent Spanish study (Colom et al. 2015). Limited-host-range coverage against all *Campylobacter* strains that may be present in the avian intestine is another potential limitation with oral administration. The use of a mixture of phages with diverse lytic spectra would be an effective solution in this case.

Escherichia coli

Among foodborne *E. coli*, STEC strains are the most commonly reported in outbreaks. Although meat and dairy products are commonly contaminated with the pathogen, fruits and vegetables have also been implicated in *E. coli*–related illness (CDC 2018). *E. coli* phages have been investigated for use in a range of applications to improve food safety. Phages have been administered orally to sheep and cattle to investigate reducing the intestinal carriage of pathogenic *E. coli*, albeit with limited success (Rivas et al. 2010, Sabouri et al. 2017). Phage preparations have also been applied with the aim of reducing *E. coli* O157:H7 numbers on cattle hides, with mixed results. The application of phage mixtures onto hide pieces in vitro caused a significant reduction in *E. coli* O157:H7 numbers (Coffey et al. 2011). However, one large-scale trial utilizing a commercial phage spray reported no significant difference in *E. coli* levels on cattle hides after phage applications. It was proposed that the large quantity of organic matter on the carcass impeded phage–host interactions (Arthur et al. 2017). Conversely, phages have been proven useful in the reduction of *E. coli* contamination on meat, milk, and vegetables but were also successful in eradicating the pathogen on ceramic, stainless steel, and polyethylene, common materials in food processing (Sabouri et al. 2017).

Further work is necessary to optimize the oral application of phages to beef animals. The best reductions of *E. coli* to date have been obtained with postharvest applications of *E. coli* phages. Accordingly, Intralytix has developed EcoShield™, a food processing aid for the control of *E. coli* on red meat (**http://www.intralytix.com**).

Salmonella

Salmonella infects or colonizes a broad range of food animals and is frequently implicated in human gastroenteritis. This bacterium can contaminate various meats and poultry, in addition to

raw milk. Fruits and vegetables have also been implicated in infection outbreaks, and control of the bacterium within the food chain is imperative (Jackson et al. 2013). *Salmonella* phages can be applied at a number of stages throughout the food production process, from the farm to processing and also during the packaging of foods. A commercial phage preparation called BAFASAL® (**http://www.proteonpharma.com**) specifies on-farm administration to poultry at the rearing stage, and the product SalmoFresh™ (Intralytix) is advertised as a food treatment for red meat, poultry, seafood, fruits, and vegetables. The efficacy of *Salmonella* phage applications has recently been reviewed (Petsong & Vongkamjan 2015).

Given that the primary reservoir of *Salmonella* is the intestine, oral phage application is considered a worthwhile endeavor. As mentioned earlier, phage encapsulation better facilitates phage survival during passage through the low stomach pH. Accordingly, Colom et al. (2015) devised a liposome encapsulation technique for delivery of *Salmonella* phages to broilers, achieving their release in the lower intestines where the bacteria reside (Colom et al. 2015). These authors subsequently demonstrated the use of alginate/$CaCO_3$ microcapsules (Colom et al. 2017). In the latter study, superior results for the delivery of phages were obtained with the capsules in comparison to nonencapsulated phages, possibly due to the additional antacid effect of the $CaCO_3$.

Listeria monocytogenes

The pathogen *Listeria monocytogenes* is ubiquitous in the environment. Seafood, soft (raw-milk) cheese, unpasteurized milk, and meat spreads are regarded as moderate- to high-risk foods for *Listeria* contamination at retail (FDA 2003). The ability of *L. monocytogenes* to grow at 4°C renders it a particular hazard in RTE foods. Nevertheless, because *Listeria* are metabolically active at 4°C, they are good targets for phage at this temperature (Back et al. 1993). Two companies have formulated phage-based products for commercial use in food. The products are ListShield™ and PhageGuard Listex™ by Intralytix and Micreos Food Safety, respectively. Although ListShield™ appears to have a wider host range (as it contains six phages compared to one in PhageGuard Listex™), both significantly reduce contamination of RTE foods and have the ability to remove *L. monocytogenes* biofilms, including those formed on common kitchen surfaces like polystyrene and stainless steel (Gutiérrez et al. 2017).

Shigella

Shigella species have been found in underchlorinated water and in a number of foods such as vegetables, fish, ground beef, potato salad, and oysters (Warren et al. 2006). The effectiveness of *Shigella* phages for biosanitation has been determined only in the past five years. In one study, *Shigella*-contaminated RTE spiced chicken was treated with a mix of three phages against *Shigella dysenteriae*, *Shigella sonnei*, and *Shigella flexneri.* This phage preparation reduced *Shigella* to below the detection limit compared with phage-free controls (Zhang et al. 2013). Since then, Intralytix has developed a *Shigella* phage preparation called ShigaShield™, which has received GRAS status by the FDA, permitting its use as a food processing aid. This five-phage mix has been tested for its efficacy in RTE foods, including smoked salmon, precooked chicken, corned beef, precut melon, yogurt, and lettuce. Upon phage application, the number of experimentally added *S. sonnei* was reduced by at least 90% in all of the tested foods. ShigaShield™ was reported to have lysed 97% of *Shigella* isolates in vitro, including multi-drug-resistant strains (Soffer et al. 2017).

Staphylococcus aureus

Enterotoxin-producing *S. aureus*, as a skin commensal, frequently contaminates foods through improper handling during preparation (Argudín et al. 2010). Ingestion can result in vomiting, abdominal cramping, and diarrhea (Kadariya et al. 2014). A number of studies have reported the isolation of several staphylococcal phages and their successes in significantly reducing the titers of *S. aureus* in different milks (García et al. 2007, 2009). It has also been shown that combining phages with high hydrostatic pressure (HHP) treatments can synergistically reduce *S. aureus* levels to below the detection limit (Tabla et al. 2012). However, given that routine pasteurization of milk eliminates *S. aureus*, the application of such phages in milks may in reality be limited. In raw milks where *S. aureus* is present, phage activity has been reported to be less efficient than in heat-treated milks (O'Flaherty et al. 2005).

Cronobacter sakazakii

Cronobacter sakazakii has been detected in a variety of food environments, but its occasional presence in powdered infant formula is the most important in the context of its ability to cause severe and sometimes fatal neonatal infections with a relatively low infectious dose (Iversen & Forsythe 2003). Although the incidence of detection is low (Muytjens et al. 1988), extended storage or temperature abuse of reconstituted infant formula can bring the pathogen, if present, to harmful levels before consumption by infants. One report investigated the biocontrol and antibiofilm potential of a three-phage mix against *Cronobacter sakazakii* and showed excellent results. Also, in different brands of infant formula, the phages brought about a reduction in levels of *Cronobacter* to below the detection limit in comparison to the phage-free controls, where the pathogen numbers exceeded 10^9 CFU/mL (Endersen et al. 2017).

Phage Control of Other Foodborne Pathogens

The use of phages to control less prominent foodborne pathogens is also being investigated. A synergistic application of a single phage and HHP completely inactivated *V. cholerae* in salmon and mussels (Ahmadi et al. 2015). In another study, the growth of *Yersinia enterocolitica* was significantly inhibited by phage treatments of contaminated pork, milk, and kitchen utensils, demonstrating their potential for yersinosis prevention (Jun et al. 2018). Phages have also been shown to effectively eliminate *Enterococcus faecalis*, an organism whose reduction in dairy products was correlated with a reduction in levels of *E. faecalis*–derived tyramine (which is associated with migraine) in dairy products (Ladero et al. 2016).

ENZYBIOTICS

At the end of the phage-infection cycle, a peptidoglycan hydrolase encoded by the phage genome called an endolysin (lysin) is produced to degrade the bacterial cell wall from within the host and allow the release of progeny phages. These endolysins encompass a diverse range of enzyme structures depending on the phage, but many of those directed at Gram-positive cells contain a catalytic domain for peptidoglycan degradation and a cell-wall-binding domain (CBD) to bind the enzyme to the substrate (Oliveira et al. 2013). As the peptidoglycan is exposed in Gram-positive bacteria, these enzymes are also effective as antimicrobials when cloned, produced, and externally applied.

Lysins offer an alternative biocontrol strategy to whole phages with additional advantages. There is no risk of transfer of genetic material and lysins can act rapidly to kill their hosts. The

enzymes generally have a broader lytic spectrum than their parent phage (Kong & Ryu 2015), apparently do not invoke resistance (Gutiérrez et al. 2014, Loeffler et al. 2003), have a short half-life and thus do not persist in the environment (Loeffler et al. 2003), and can lyse cells within biofilms (Gutiérrez et al. 2014).

Recombinant *S. aureus* phage lysins are among the best studied. In milk, these lysins in their native form have proven their ability to reduce *S. aureus*, either alone or synergistically with nisin or carvacrol (Chang et al. 2017b, García et al. 2010, Obeso et al. 2008). Chimeric *S. aureus* lysins have demonstrated even more enhanced antibacterial activity. Schmelcher et al. (2012) constructed a chimeric staphylococcal lysin, fusing the catalytic domain of phage λSA2 lysin with alternative CBDs. One chimeric lysin retained activity in milk for the duration of a three-hour *S. aureus* reduction experiment in milk, resulting in reduced *S. aureus* counts in comparison to lysin-free controls (Schmelcher et al. 2012). The staphylococcal lysin LysSA11, in addition to displaying concentration-dependent antibacterial efficacy in milk, was also demonstrated to reduce MRSA contamination of ham and could completely eliminate the pathogen on propylene and steel food preparation surfaces (Chang et al. 2017a). Veterinary applications are also possible with *S. aureus* lysins. In cases of bovine mastitis caused by *S. aureus*, intramammary infusions of endolysin trx-SA1 reduced bacterial numbers and restored the milk to its normal appearance (Fan et al. 2016).

Listeria lysins also show great potential in food safety applications. The lysin PlyP100 appears to be stable in cheese for up to four weeks and exhibited synergistic antilisterial effects when combined with nisin (Ibarra-Sánchez et al. 2018). In addition, Misiou et al. (2018) have recently reported that the combination of HHP with the lysin PlyP825 was able to completely eradicate *Listeria* in 89% of milk and mozzarella samples tested (Misiou et al. 2018).

Production and secretion of phage lysins in eukaryotic systems have been demonstrated in transgenic plants. *Clavibacter michiganensis* subsp. *michiganensis* (CMM) is a Gram-positive plant pathogen. The lysin of CMM phage CMP1 was transformed (via *Agrobacterium*-mediated transformation) in the tomato plant *Solanum lycopersicum*, which was subsequently cultivated. CMM survival was reduced in plant homogenates in comparison to lysin-free controls, and transgenic leaves were more resistant to wilting upon CMM application (Wittmann et al. 2015).

Streptococcal phage lysins, including λSA2 and B30, have also been cloned, which have been found to exhibit a synergistic lytic effect on *Streptococcus dysgalactiae*, *Streptococcus agalactiae*, and *Streptococcus uberis* in milk. In a murine mastitis model, these lysins also succeeded in significantly reducing pathogen loads upon intramammary infusion (Schmelcher et al. 2015). In the genus *Clostridium*, a thermostable phage lysin was developed for intended use in poultry feed (Swift et al. 2015). In addition, the *Clostridium* phage lysin CP25L was secreted from *Lactobacillus johnsonii*, resulting in *Clostridium perfingens* reduction in small-scale static cocultures (Gervasi et al. 2014).

In the case of Gram-negatives in which external lysin access to the peptidoglycan is prevented by the outer membrane, Artilysins® were developed. These engineered lysins have amino acid sequences that can destabilize the outer membrane and access the peptidoglycan to induce cell lysis (Larpin et al. 2018). The potential of their use in animal feed and veterinary applications against Gram-negative pathogens is currently under investigation by the company LYSANDO AG (**http://www.lysando.com**) (Gerstmans et al. 2016).

Endolysins are not the only lytic enzymes associated with phages. At the beginning of phage infection, the virion-associated peptidoglycan hydrolase (VAPGH) or ectolysin locally degrades the peptidoglycan enough to allow for DNA injection into the host cytoplasm. These ectolysins have not received as much attention in comparison to endolysins, but their potential as antimicrobials has been demonstrated (Channabasappa et al. 2017).

OTHER APPLICATIONS OF PHAGES AND THEIR COMPONENTS IN FOOD

In addition to antibacterial applications, phages can be employed for detection of undesirable bacteria and pathogens and also incorporated into food packaging and processing surfaces for food-related biocontrol. The scope of their use is constantly widening, and phage-based pathogen-detection strategies are becoming more and more innovative (Anany et al. 2017).

Whole Phages for the Detection of Foodborne Pathogens

Phage amplification assays are one of the simplest, yet most specific, methods of host detection. The test sample is combined with phages to allow for bacterial attachment, and an increase in phage titer correlates with successful infection of the target bacterium. Phage amplification, as opposed to direct PCR or other detection methods of bacteria, ensures that only live cells are identified. *Mycobacterium avium* subsp. *paratuberculosis* phages have been detected following their amplification in milk and infant formula using phage-specific PCR (Botsaris et al. 2013, 2016). Detection of phage amplification from foodborne pathogens has also been accomplished using quantitative real-time PCR (qPCR), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-MS), and immunochromatography (Madonna et al. 2003, Stambach et al. 2015).

Another phage-based detection system focuses on the release of intracellular markers from phage-infected host cells. Intracellular adenylate kinase is released from host cells upon phage infection and lysis. In the presence of excess ADP, adenylate kinase catalyzes the generation of ATP, which can be exploited to generate a bioluminescent reaction. The quantified light emissions are proportional to initial bacterial numbers. This method was successful in identifying *E. coli* 0157:H7 in ground beef using a short enrichment step (Kannan et al. 2010).

Another phage-based biodetection method is based on reporter phages carrying bioluminescence genes. Upon infection of a viable host, these genes are expressed, resulting in the emission of a detectable signal. The gene for the luciferase NanoLuc was introduced into the genome of *E. coli* prophage φV10, and upon host infection in the presence of a substrate, a signal was detectable via a luminometer. In this case, a measurable signal was produced after a nine-hour incubation of φV10 with *E. coli* 0157:H7 in a homogenized beef broth, when the cell count was just 4.68 CFU/40 mL (Zhang et al. 2016). Similar methodologies using luciferase-based emissions have also been successful in confirming *Listeria monocytogenes* and *Salmonella* species contamination in foods such as lettuce, raw meat, soft cheeses, and eggs, with slightly varying sensitivities based on the complexity of the food matrix (Chen & Griffiths 1996, Loessner et al. 1997).

Phage–host binding can also be a useful bacterial detection mechanism if the phage has been prelabeled. The detection of STEC in spinach and lettuce was achieved via Phazyme assays, whose developers claimed that the protocol was suitable for field-based diagnostic testing. In this work, sample swabs were incubated with immunomagnetic STEC-specific beads, horseradish peroxidase–labeled phage, and a luminescent substrate, and results were obtained following an eight-hour incubation (Willford et al. 2011).

A phage-based technique for in situ pathogen detection has also been developed that utilizes a ferromagnetoelastic (FME) biosensor composed of an FME platform containing bound phages. If the biosensor was placed on food with the bacterial host present, phage binding caused a rapid resonant frequency shift of the platform, the intensity of which directly correlated with the amount of bound pathogen. Using this device, *S.* Typhimurium detection in cantaloupe was reported to display superior sensitivity to qPCR (Park et al. 2013). The system has also been demonstrated for *B. cereus* detection (Choi et al. 2018).

Phage Components for Pathogen Detection in Food

Both the CBD of a phage lysin and the phage receptor binding protein (RBP) demonstrate host specificity, which has successfully been exploited as a means of bacterial identification. These specific binding proteins attach to bacterial cells, facilitating their separation from food matrices. Alternatively, the binding proteins themselves can be labeled for real-time detection of specific bacterial pathogens in foods. The application of binding proteins associated with lysins (CBDs) for detection is limited to Gram-positives, as these CBDs require direct peptidoglycan access.

Phage-based separation of bacteria from food has been developed using host-specific phage proteins. When paramagnetic beads coated with the RBP of *Salmonella* phage S16 were tested for *Salmonella* cell capture from artificially inoculated celery, sprouts, chicken, infant formula, and milk, the bacterium was successfully recovered following pre-enrichment of samples that had been inoculated with as low as 10 CFU/25 g. These authors also developed bead-bound horseradish peroxidase–conjugated RBP proteins for enzyme-linked detection by a colorimetric assay (Denyes et al. 2017). This phage-based method was reported to be superior to immunomagnetic separation because of occasional cross-reactivity of antibodies with other nontarget pathogens in the latter approach (Kaclíková et al. 2001, Muldoon et al. 2007).

Fluorescent tags have recently been combined with phage RBPs and CBDs, and these have been applied for rapid real-time identification of foodborne bacteria. This approach showed impressive success when different fluorescent proteins and CBDs with varying *Listeria* host affinities were combined (Schmelcher et al. 2010). A similar approach was used to successfully detect *Clostridium tyrobutyricum* spores directly from cheese samples (Gómez-Torres et al. 2018). This technology has been developed by BioMérieux in the form of the VIDAS® UP kit, which has been applied to detect *Salmonella*, *Listeria*, and *E. coli* 0157 from food (**http://www.biomerieux.com/**).

Phage CBDs and RBPs have also been incorporated into biosensors in a manner similar to whole-phage-based FME biosensors discussed in the previous section. The advantages of using specific phage proteins over whole phages are their smaller size and increased density in sensor platforms and the avoidance of phage infection and bacterial lysis after recognition (Vinay et al. 2015). This technology has been applied for *Listeria* detection from milk samples, and a similar biosensor has been developed for *Salmonella* with impressive sensitivity (Tay et al. 2012, Tolba et al. 2012).

Phage-Based Active Food Packaging

The term active packaging refers to the incorporation of an agent within a packaging material that fulfills a role in food preservation or product quality extension (Kerry et al. 2006). Accordingly, phages as the active agent have been incorporated into a number of materials intended for food packaging. *Salmonella* phages were successfully incorporated into biodegradable cellulose acetate films, causing an inhibition of *Salmonella* growth when placed on growing cultures (Gouvêa et al. 2015). *Salmonella* phages were also incorporated into an edible xanthan-based coating for packaging films that could inhibit *Salmonella* growth on RTE meat for more than 30 days (Radford et al. 2017). In the context of binding phages to surfaces, indium tin oxide was shown to be a successful conjugation material for the binding of T4 phages (Liana et al. 2018).

The physical and pH vulnerability of phage structures on such materials led to another interesting development in which the phages were stabilized on filter papers containing either carboxylic acid or amine groups. This technology was demonstrated to permit phage activity between pH 5.6 and 14 (Meyer et al. 2017).

Phages as Indicators for Enteric Viruses and Bacteria in Foods

Specific phages associated with intestinal bacteria can be used as an indicator for human enteric virus contamination of foods because of their similarities regarding environmental persistence and stability during treatment processes. The presence of F pili–infecting RNA coliphages and *Bacteroides* phages on shellfish has been shown to be a good indicator for the possible presence of enteric viruses on this material (Hartard et al. 2018). These coliphages and other enteric phages have also proven useful in monitoring the virological and bacteriological safety of ground beef and poultry during processing (Hsu et al. 2002).

CONCLUDING REMARKS

Although phages can be considered troublesome to the food industry, given their ability to cause fermentation failures and promote the emergence of new bacterial pathogens through the transduction of virulence genes, they are increasingly being recognized as a potential solution to a variety of issues such as the detection and biocontrol of various undesirable bacteria that cause either infectious diseases or spoilage of food materials.

The diversity of the applications of phages and their encoded proteins has been discussed above, but there are still potentially unexploited opportunities for applications of these ubiquitous natural agents in the general area of detection and control. This is at a time when the use of traditional artificial chemical preservatives is discouraged by consumer attitudes. It is reasonable to expect that the focus of phage research would initially be directed toward the more prominent pathogens. But as these applications continue to be demonstrably successful and financially worthwhile for those developing them, phages are likely to be further applied for the less prominent but nevertheless still significant pathogens and spoilage organisms. These newer developments will need to take into account diverse technical hurdles that may be associated with certain food matrices or particular behaviors of specific bacterial pathogens.

Although there are some well-recognized possible pitfalls in the use of phages in food applications, such as the loss of bioactivity, reduced activity at extremes of pH, scarcity of host bacterial cells in the application area, and limited lytic spectra of some phages, innovative solutions, including phage encapsulation, the addition of apathogenic hosts to boost phage titers, and the use of multiple phages to increase the host range, are constantly being developed. Phage endolysins have also been explored and engineered for food applications, an endeavor that is already beginning to complement the existing battery of phage-based biocontrol and detection applications. Indeed, the area of phage-based detection of bacterial pathogens is continuing to see significant and interesting advances. Some of the phage-based sensor technologies discussed in this review have even reported superior sensitivity and more rapid results than qPCR.

With this progress, it is very likely that these detection methods will be more widely used in both laboratory and field diagnostic kits in the future. The body of phage knowledge has expanded greatly in recent years and will inevitably continue to do so, exploring not-yet-conceived avenues for useful applications in the food industry.

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