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Review Article

Application of Bacteriophage in Biocontrol of Major Foodborne Bacterial Pathogens

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Abstract

Bacteriophages are viruses of bacteria that can be applied as pre-harvest and post-harvest interventions in food to reduce the foodborne pathogens. The increasing incidence of foodborne illnesses and prevalence of antibiotic-resistant bacteria have led to the use of phage as an alternative biocontrol agent in food industry to assure the safety of the food products. A number of studies have shown the potential of bacteriophages in controlling various foodborne pathogens within food animals and also the raw and processed foods. This paper reviews the potential use of bacteriophages in biocontrol of the major foodborne bacterial pathogens (*Salmonella*, *Campylobacter*, *E. coli* O157: H7 and *Listeria monocytogenes*) in food animals and food processing. Furthermore, the advantages and limitations of bacteriophages as biocontrol agent in foods were described in this paper as well.

Keywords: Bacteriophage; Biocontrol; Foodborne; Pathogen

Introduction

The increased incidence of foodborne illness has caused substantial morbidity and mortality worldwide annually, often associated with outbreaks and food contamination. According to Centers for Disease Control and Prevention [1], foodborne illness is known to be a ubiquitous, costly, yet preventable public health concern. In 2013, the Foodborne Disease Active Surveillance Network (FoodNet) identified 19,056 cases of foodborne infection with approximately 4,200 hospitalizations and 80 deaths in United States [2]. However, the statistical data of foodborne illness on a global scale is fragmented due to the unrecognized or unreported outbreaks particularly in the developing countries [3].

World Health Organization stated that food safety remains a continuous challenge to everyone especially in the management of both infectious and non-infectious foodborne hazards [4]. Despite the current effective technologies and the good manufacturing practices, the food safety is constantly threatened by the factors related to changes in lifestyle, consumer eating habits, food and agriculture manufacturing processes and also the increased international trade [5]. Foodborne disease can be attributed to a wide range of microbes such as bacteria, viruses and parasites as showed in Table 1.

Generally, foodborne diseases are associated with acute, mild and self-limiting gastroenteritis with symptoms such as nausea, vomiting and diarrhea as a consequence of consumption of microbial contaminated food [6]. Besides that, a number of chronic sequelae may result from foodborne infections involving diseases that affect the cardiovascular, musculoskeletal, and respiratory and immune systems [6].

Bacterial antimicrobial resistance has become a public health concern as the increased of antibiotic resistant bacteria poses increasing threat to human health [7,8]. There is need for development of novel non-antibiotic approach to fight against the increased incidence of multi-drug resistant pathogen due to the shortage of new antibiotics in developmental pipeline [9]. Recently, there has been an increased interest in the application of bacteriophage as an alternative antimicrobial chemotherapy in various fields including human infections, food safety, agriculture, and veterinary applications [10]. However, due to the long product development and approval timelines for clinical use of phage therapy, many companies have followed food safety, agricultural and industrial applications alternatively. Despite the increasing antibiotic resistant strains, consumer demands for food products which are free from foodborne pathogens and synthetic chemicals have further encouraged many companies to involve in the development and production of phage-based products for food safety applications.

In this review, it concentrates on the applications of bacteriophages as biocontrol agents against the 4 major pathogenic foodborne bacteria, namely *Esherichia* coli O157:H7, *Salmonella, Campylobacter* and *Listeria monocytogenes* in the food animals (preharvest) and food products (postharvest) as well as highlighting the advantages and drawbacks of phage therapy in food safety.

Emergence of antibiotic resistant bacteria

Overview: There was a big revolution in medical field in the 1940s where antibiotics were introduced for the treatment of various infectious diseases. The discovery of antibiotics has dramatically changed the outcome of common human diseases whereby most of the deadly illnesses became readily treatable [11]. The wide use of antimicrobial agents in agriculture such as livestock and poultry has been started since the 1950s [12]. In United States, at least 17 antimicrobials were allowed to be used in food animals whereas all the antibiotics licensed for human were used in Europe as well. Antibiotics had been widely employed in the food animals therapeutically, prophylactically and also non-therapeutically to improve feed-efficiency. The exceeding use of antibiotic for non-therapeutic purposes in food animals has become a major public concern as this can lead to the decline of effective antibiotics used for

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Table 1: Foodborne pathogens associated with outbreaks from contaminated food [107].

Bacteria	Virus	Parasite
Bacillus cereus	Astrovirus	*Cryptosporidium parvum*
Campylobacter jejuni	Hepatitis A virus	*Entamoeba histolytica*
Clostridium botulinum	Hepatitis E virus	*Taenia solium*
Escherichia coli	Norovirus	*Toxoplasma gondii*
Listeria monocytogenes	Rotavirus	*Trichinella spiralis*
Salmonella enterica		
Vibrio cholerae		
Vibrio parahaemolyticus		
Vibrio vulnificus		

treatment of bacterial infections in human. As the antibiotics being employed in the food animal are often similar classes as those used for human such as tetracyclines, macrolides and fluoroquinolones [13]. Hence, the abuse and uncontrolled using of antibiotics particularly in the food animal and agriculture sector is the main factor causing the emergence of multi-drug resistance bacteria and the dissemination of the antibiotic resistance genes. The multi-drug resistant pathogens not only affect the animal health, they also affect public health via transmission to human as foodborne contaminants.

Antibiotic resistant food borne pathogens: There are various routes for the food to be contaminated with antimicrobial resistant bacteria. For instance, the presence of the antimicrobial resistant bacteria on the food animals can be resulted by fecal contamination during slaughter. The contaminated water with fecal materials may aid in the transmission of the antimicrobial resistant bacteria to food products during production or even after processing which is referred as post-contamination [14]. Hence, the presence of antibiotic resistant bacteria in the food animals can be easily transmitted to human through consumption or even direct contact with the food animals. These types of acquisition of antibiotic resistant foodborne pathogens by human have been reported by other researchers [15]. Pathogens such as *Salmonella* Typhimurium definitive phage 104 [16], fluoroquinolone-resistant *Campylobacter jejuni* [17], multi-drug resistant *Listeria monocytogenes* [18] and certain toxigenic *E. coli* strains present in the livestock and food products are transmitted to human through the food chain. Epidemiology studies showed that there is an association between the antibiotic used in the animal feed with the subsequent isolation of the resistant pathogens from the similar animals. For instance, the recovery of a ceftriaxone-resistant isolate of *Salmonella enterica* from a sick child was the same from an isolate from cattle [19].

Infection with multi-drug resistant bacteria in human is definitely more difficult to be treated and caused severe harm to immunocompromised patients. The emerging antibiotic resistance of *Salmonella* and *Campylobacter* spp. resulted in significant increase in hospitalization and the risks of invasive infections and death [20,21]. Moreover, multi-drug resistant bacteria could spread to countries far way with the increasing growth of the international trade of the food animals.

Bacteriophage

Historical background about bacteriophage: Bacteriophages are viruses discovered independently by Frederick Twort and Felix d'Herelle during early 20th century [22-24]. Due to their remarkable antibacterial potency, bacteriophages were implemented in the treatment of human diseases almost instantly after their discovery. They were appeared as the frontline therapeutics against infectious disease before the discovery of the broad spectrum antibiotic and were used in various countries until The Second World War [24]. The clinical use of phages as therapeutic agents and phage research started to declined and eventually ceased due to the limited knowledge of phage properties and contradictory results from various published studies. The therapeutic use of bacteriophage was further dampened after the emergence of age of antibiotic chemotherapy with the introduction of sulfa drugs in 1930s and penicillin in 1940s [10]. However, the phage research and development still remained active in former Soviet Union and Poland [25]. Interestingly, the therapeutic value of bacteriophage has been reconsidered over the last decade due to the emergence of multi-drug resistant bacteria. Therefore, the therapeutic value of bacteriophage in various areas ranging from food safety to prevention and treatment of bacterial diseases are being reconsidered [26,27].

Biology of bacteriophage: Bacteriophages are bacterial viruses that only infect and multiply within their bacterial hosts with high host specificity of strain or species level [28]. Structurally, they contain a core nucleic acid encapsulated with a protein or lipoprotein capsid which is connected with a tail that interacts with various bacterial surface receptors via the tip of the tail fibers. This interaction shows an affinity that is specific to certain group of bacteria or even to a particular strain [26]. Phages are extremely diversified group and they are known to be the most abundant and self-replicating organisms on Earth (approximately 10^{30}-10^{31} particles compared to 10^{7} humans) with the fact that they are ten times more than their bacterial host [29,30]. Most of the phages are tailed bacteriophage, which accounts for 96% of all phages present on earth, belonging to the order *Caudovirales* [31]. According to International Committee on Taxonomy of Viruses, they are classified into three families: the *Myoviridae* (long contractile tail), the *Siphoviridae* (long non-contractile tail) and the *Podoviridae* (short non-contractile tail) [32].

Life cycle of phage: As the natural parasites of bacteria, bacteriophages start the infection in bacterial host with adsorption to the suitable host cell reversibly with specific cell-surface proteins and followed by injecting their genetic material into the cytoplasm [24]. Typically, different phages display different life cycle with the bacterial host after surface adsorption and introduction of viral genetic material. It can be classified into two broad categories which are the lytic (virulent) cycle or the lysogenic (temperate phage) cycle. The virulent bacteriophages, which undergo the lytic cycle, capable to induce host cell lysis upon infection. In detail, after binding and injection of its DNA into the host cell, the virulent bacteriophages hijack the host cell's protein machinery via the expression of specific enzyme encoded by phage genome which redirects the bacterial synthesis machinery to reproduction of the new phage particles. The production of phage's enzyme in the later stage such as lysins and holins induce destruction of the cell membrane allowing the newly formed virion burst out from the lysed bacterial host cell to the extracellular environment [33].

Meanwhile, the temperate phage, in addition to being capable to enter lytic cycle, possesses the ability to persist as a prophage in the genome of their bacterial host in the lysogenic cycle. The phage genome remains in a repressed state in the host genome and is replicated as part of the bacterial chromosome until lytic cycle is induced. Hence, temperate phages are not suitable for direct therapeutic use as it may mediate transduction by transferring genetic material of one bacterium to another. This process may lead to the development of antibiotic resistance or even increased virulence of the host by acquiring genes from the prophage. Only the lytic bacteriophages, which replicate exponentially and eradicate the bacteria rapidly regardless of their antibiotic resistance profile, are more suitable for the biotherapy purposes and they are possibly one of the most harmless antibacterial approaches available [27]. Meanwhile, rather than relying on the killing ability, the unique characteristic of temperate phage which able to deliver genetic material into the host genome has been exploited and demonstrated in a system that restores antibiotic efficiency by reversing the resistance of the bacterial host, making them susceptible to antibiotics again [34].

Applications of bacteriophage in food industry

There are many reviews about the potential use and current limitations of the applications of phages in clinical use [26], agriculture, veterinary biocontrol, food safety [35] and also diagnostic applications [36]. However, this review shall focus on the potential of phages in the control of foodborne pathogens. Bacteriophages have been widely used as natural antibacterials to control food pathogens and studies have shown that phage biocontrol in food demonstrated promising results. Phage therapy has been shown to be effective as both preharvest and postharvest interventions to control wide range of foodborne pathogens such as *Salmonella* spp. [37], *Campylobacter* spp. [38], *Listeria* spp. [39] and *Escherichia* spp. [40]. With the current concern over the emerging of antibiotic resistant foodborne pathogen resulted from the abuse and misuse of antibiotics, bacteriophages could serve as an alternative antimicrobial in the food industry.

The use of bacteriophage as a preharvest strategy is to prevent animal illness and also to reduce the pathogens carried by the livestocks via direct administration of phages. Meanwhile, postharvest strategies involve the use of bacteriophages on animal carcasses to remove unwanted contaminants on the products.

Control of foodborne pathogens in animal production and food products: In the preharvest interventions, the phages are usually administrated directly to the live 'food animals' before being processed into meat. The purpose of such approach is that bacteriophages may eliminate or reduce the colonization of the pathogenic bacteria on the livestock prior to slaughter and carcass processing to ensure that the processed meat is free from those pathogens. The potential benefits of bacteriophage in controlling and eliminating the pathogenic bacteria in livestocks have been investigated in various studies using poultry, swine, sheep and cattle as the in vivo model to evaluate the efficacy of the bacteriophages. *Salmonella*, *Campylobacter* and *E. coli* O157:H7 are the common contaminants of livestocks and they are carried in the intestinal tract of the animals asymptomatically. They are usually transmitted to other livestocks and food supply through the shedding in fecal materials of the carrier. Meanwhile, phage-based technologies in the control of foodborne pathogens in postharvest foods appeared to be more successful than those phage therapies in preharvest foods. The postharvest intervention is to improve the food safety by applying phages on the surface of foods, hence eliminate or reduce the contamination of foods with foodborne bacterial pathogens, making the foods safe to consume.

Escherichia coli O157: H7: *E. coli* is a gram-negative bacterium and attributed a third of cases of childhood diarrhea in developing countries. Furthermore, it is also known to be the prominent cause of traveler's diarrhea and associated with diarrhea in domestic and pet animals. The emergence of *Escherichia coli* O157:H7 is still a public health concern since its first outbreak in 1982 which was associated with the consumption of hamburgers [41]. Serotype O157:H7 is referred as a Shiga toxin-producing *E. coli* which is classified under the enterohemorrhagic *E. coli* (EHEC) strain that produces two types of toxins: Shiga toxin 1 (Stx-1) and Shiga toxin 2 (Stx-2). It causes a wide spectrum of disease ranging from mild diarrhea to haemorrhagic colitis, haemolytic uremic syndrome and thrombotic thrombocytopenic purpura [42].

The main reservoirs of *E. coli* O157:H7 are comprised of ruminants such as cattle and sheep, as it does not induce significant clinical symptoms and survive well in the intestinal conditions of the ruminants. The main route of transmission to human is via uncooked contaminated meats particularly when care is not taken during the slaughtering process leading to contamination of the meat with the intestinal contents, fecal materials or dirt on the hide of ruminants.

The preharvest control of E. coli O157:H7: Most of the recent phage therapies to *E. coli* were conducted on ruminants such as cattle and sheep. One of the most recent in vivo studies was to evaluate the efficacy of a newly isolated O157:H7-infecting phage named CEV2, found naturally in gastrointestinal tracts of ruminants, in the reduction of *E. coli* O157:H7 in sheep [43]. It has found that cocktail of CEV2 and a previously isolated phage CEV1 achieved more than 99.9% reduction of *E. coli* levels in the intestinal tracts after administration orally into the in vivo sheep model, this result suggests that phage cocktails are more efficient than an individual phage in the removal of O157:H7 gut colonization via oral delivery [44]. This result is further supported by the use of a cocktail of KH1 and SH1 bacteriophages in a combined oral rectal treatment were able to reduce the *E. coli* O157:H7 levels from the cattle but no total eradication was observed [45].

In 2010, Rivas et al. [46] examined the efficacy of bacteriophages e11/2 and e4/1c on the reduction of *E. coli* levels in cattle. They found out that both e11/2 and e4/1c significantly reduced the *E. coli* O157:H7 levels in an *ex vivo* rumen model. There was also rapid reduction of *E. coli* O157:H7 in the animals within 24 to 48 hours but no reduction in fecal shedding. Besides that, both of these bacteriophages showed potential in the reduction of *E. coli* O157:H7 present in cattle hide [47].

Although studies above demonstrated the potential of bacteriophages to control foodborne pathogen in livestock, there are still some disadvantages that need to be considered. For instance, majority of the researchers suggested that oral treatment is not effective in reducing *E. coli* levels particularly in the fecal shedding. Several speculations have been made based on the failure of oral delivery of phages in the reduction of the pathogen. It may be due to the nonspecific binding of the phages to other substances such as food particles in the intestinal tract, the acidic conditions in the abomasum of the livestock may inactivate the phages leading to insufficient phages that manage to reach the target site [48,49]. Meanwhile, Stanford et al. [49] managed to address this complication by introducing encapsulated phages which able to reduce the shedding levels for 14 days.

Studies on the postharvest control of Escherichia coli O157:H7: Researchers have demonstrated that most of the postharvest interventions using bacteriophages were successful in reducing the *E. coli* O157:H7 levels in various food products such as meat [40], vegetables [50, 51] and processed foods [52]. O'Flynn et al. [40] evaluated the efficacy of three phages (e11/2. E4/1c and PP01) to lyse the *E.coli* O157:H7 on meat individually and in cocktail form. They have shown that these three phages are effective in killing the *E. coli* O157:H7 with seven out nine samples that devoid of the pathogens after treatment while less than 10CFU/mL observed in the remaining samples. Furthermore, the combination of phages with other food-grade antimicrobial able to achieve a higher reduction of *E. coli* O157:H7, the combination phages with *trans*-cinnamaldehyde oil achieved a complete inactivation of *E. coli* O157:H7 [50]. Other than the application of phages in reducing contamination of foods, phages are also useful for decontamination of hard surfaces as cross-contamination via food contact surfaces to food is a primary concern in food industry. Abuladze et al. [52] utilized a three phage cocktail (ECP-100) to decontaminate the hard surfaces found in food production facilities such as glass and gypsum. The ECP-100 achieved a significant 4 log reduction of *E. coli* O157:H7 recovered from the hard surfaces.

Salmonella spp. and Campylobacter spp: Many studies about phage therapy applications to foodborne pathogens have been conducted in poultry. *Salmonella* spp. and *Campylobacter* spp. are the common pathogens that found in contaminated poultry and they are the top two world's most prominent foodborne pathogens which cause salmonellosis and campylobacteriosis respectively in humans. *Salmonella* is a genus of gram-negative facultative intracellular bacteria which has caused an estimated 93.8 million illness worldwide and approximately 155,000 deaths annually [53]. *Salmonella enterica* serovars Enteritidis and Typhimurium are still the most prevalent *Salmonella* serovars and responsible for majority of the outbreaks which are often associated with consumption of contaminated eggs, poultry, swine and cattle meats. Salmonellosis results in diarrhoea, fever, vomiting and abdominal cramps in humans. Besides infection in human, salmonellosis can occur in swine and is known to be the top 10 most common disease in farm pig, thereby costing the pork producers approximately $100 mil each year [54]. Meanwhile, *Campylobacter* is a genus of gram-negative microaerophilic bacteria which grow optimally at 41^{O}C. *C. jejuni* and *C. coli* are both the *Campylobacter* spp. that responsible for majority cases of bacterial gastroenteritis in humans. It has been suggested that *Campylobacter* spp. is the most common enteric pathogen with 2.4 mil cases of *C. jejuni* and others species were found annually in United States.

Campylobacteriosis is also the most commonly reported zoonosis in Europe followed by salmonellosis with a total of 190,566 cases reported in 2008 [55]. It is often resulted from consumption of contaminated poultry products or cross-contamination from other uncooked foods. According to European Food Safety Authority [56], *Campylobacter* spp. colonizes 80% of the poultry in the UK as intestinal flora and is often present in the contents of the caecum region with relatively large number of approximately 7 log_{10} CFU g^{-1} [57, 58]. Therefore, the release of the intestinal contents from the poultry carcasses during slaughtering and processing resulted in contamination of the meat for human consumption is inevitable [58,59].

Studies on the preharvest control of Salmonella spp: Some researchers demonstrated the use of bacteriophage as a preharvest intervention to decrease *S. enterica* concentration in poultry [60-62]. The administration of phage prior to infection and the continuous dosing of phage are able to achieve a significant reduction of *Salmonella* in the animals over time [62]. Bardina et al. [62] used a cocktail of three bacteriophages (UAB_Phi20, UAB_Phi78 and UAB_Phi87) against *Salmonella enterica* serovar Enteritidis and Typhimurium in both mouse and chicken. The cocktail treatment achieved a 50% survival of the mouse model when it was administered simultaneously with infection and at 6, 24 and 30 h post-infection. A more significant reduction of *Salmonella* concentration in chicken cecum was observed when the cocktail was administered a day before infection and followed by continuous dosing after infection [62]. These results were supported by other studies [60] in which cocktails of 4 different phages (CB4Ø) and 45 bacteriophage isolated from wastewater plant (WT45Ø) showed a significant reduction of *S. enterica* serovar Enteritidis in cecal tonsils of chicks after 24h post-infection but persistent reduction was not observed after 48h post infection, suggesting that continuous dosing is required to sustain the efficacy of bacteriophage in reducing *Salmonella* colonization in poultry. Furthermore, several studies based on the combination use of bacteriophage and competitive exclusion products have been performed to reduce *Salmonella* colonization in experimentally induced chickens [63, 64].

These studies concluded that the combination of both types of biocontrol agents (bacteriophage and exclusion products) can be an effective approach to reduce *Salmonella* colonization in poultry. Interestingly, bacteriophage therapy can play a role in preventing horizontal transmission of the *Salmonella* between livestock. Lim et al. [65] showed that ϕCJ07, a virulent bacteriophage, resulted in significant decrease in intestinal colonization of *S. enterica* serovar Enteritidis in both infected chicks and the uninfected co-habitating chicks. Besides the studies on phage therapy in poultry, some reported the potential of bacteriophage as preharvest intervention to control *Salmonella* in swine. As *Salmonella* Typhimurium has been a significant pathogen of pig, causing $100 mil loss in pork producer annually. Many studies showed that phage cocktail resulted in reduction of *Salmonella* in various organ contents such as cecal [66], rectal [67] and tonsil of pigs [68]. Several approaches of administration of phage in different formulations, microencapsulated phage or phage suspension, to control and reduce *Salmonella* in swine were evaluated as well [66-68].

Studies on the postharvest control of Salmonella spp: In the postharvest control of *Salmonella,* studies were conducted on foods which are commonly contaminated with *Salmonella* such as chicken skin, pig skin, egg products, and cheese [69,70]. One recent study demonstrated bacteriophage cocktail and chemical agents such as dichloroisocyanurate, peroxyacetic acid and lactic acid were used to control *S.* Enteritidis on chick skin under stimulation of an industrial condition [71]. They have concluded that bacteriophages may be employed as an alternative biocontrol agent for *Salmonella* in poultry industrial setting due to the similar efficacy of the bacteriophage demonstrated in reducing the *S.* Enteritidis on chicken skin when compared to other chemical agents [71]. Meanwhile, the application of F01-E2 phage followed by 8°C storage successfully eradicated *S.* Typhimurium in a variety of ready-to-eat foods such as turkey deli meat, chocolate milk, cooked and chilled seafood and hotdogs [72]. The biocontrol potential of bacteriophage against *Salmonella* on freshly-cut fruits was assessed and phages showed a greater reduction of *Salmonella* on fresh-cut melon than the use of chemical sanitizers, but no significant reduction of *Salmonella* was observed on the contaminated apple slices [73].

Studies on the preharvest control of *Campylobacter* spp: Majority of the biocontrol studies of bacteriophages against *Campylobacter* spp. were conducted in poultry. Loc-Carrillo et al. [74] were the first to perform bacteriophage treatment of chicken and discovered effective reduction of *Campylobacter* counts in cecal contents in the treated broiler chickens. Similarly, Wagenaar et al. [75] demonstrated that the combined phages approach provided a greater decrease in *Campylobacter* level in the cecal contents of infected broiler chickens than single-phage approach [75]. These observations are in agreement with others that showed the colonization of both *C. jejuni* and *C. coli* in chickens were successfully reduced upon the exposure to virulent bacteriophages [76, 77].

Studies on the postharvest control of *Campylobacter* spp: In addition to therapy applications, several studies on postharvest interventions of bacteriophages against *Campylobacter* were conducted to control pathogens contamination on the food surfaces such as chicken skin [38,78]. Although both of the studies showed a small reduction of *Campylobacter* levels on the chicken skin, Atterbury et al. [78] improved the action of bacteriophage to achieve a greater reduction with the combination of freezing at -20°C.

Listeria spp.

Listeria monocytogenes is a gram-positive opportunistic human pathogen. It is widely distributed in the environment and foods as it is well adapted to different environmental conditions of food matrices including tolerance to high salt levels, low pH (<6), low oxygen as well as low temperature [79]. Hence, it is often associated with contaminated minimally processed foods and only 10^3CFU/mL of *Listeria monocytogenes* needed to cause listeriosis, an invasive infection in human. It afflicts an estimated of 2,000 hospitalizations and 500 deaths annually in United States [15]. Despite its low incidence, the high mortality rate of 15-40% of listeriosis is still a great concern, making it a prominent pathogen [80]. Listeriosis results in several diseases such as septicaemia, meningitis, encephalitis and even miscarriage in pregnant women. *L. monocytogenes* is commonly isolated from ready-to-eat food such as vegetables, dairy products and cold-cut poultry or from cross contaminated foods being stored in refrigerated temperature [79].

Studies on the postharvest control of Listeria spp: Due to its ubiquitous nature and the ability to contaminate various foods, the phage treatments of *Listeria* spp. often concentrate on the postharvest applications. The first study of bacteriophage therapy on *Listeria* spp. was reported on 2002 by using a listeriophage on *L. monocytogenes* in combination with a bacteriocin, called nisin [39]. Moreover, Leverentz et al. [81,82] further demonstrated that phage cocktail in combination with bacteriocin able to reduce *Listeria* spp. on fresh produce such as freshly-cut melon. However, *Listeria* phage showed reduced stability and efficacy in reducing the pathogen on apple slices, suggesting that inactivation of phage occurs at low pH. A complete eradication of *Listeria* spp. by a virulent phage P100 was reported, the study evaluated the efficacy of phage to control *Listeria* spp. on cheese [83]. Meanwhile, Guenther et al. [69] demonstrated the effectiveness of a bacteriophage cocktail (P100 and A511) to control *L. monocytogenes* in various ready-to-eat foods regardless of the different storage time and temperature. Other studies also showed that phages can be an effective biocontrol agent against *L. monocytogenes* in processed fish meat and poultry products [84,85].

In summary, the total eradication of the pathogens colonizing the intestinal tract of the animal, which possessing the complex and highly dynamic microenvironment, may not be achieved easily by the use of bacteriophage alone. As compared to the treatment of the animal products after slaughtering, the number of the bacteria is usually very high in the intestine of the animals. Although reduction of pathogen prior to slaughter provides more safety for consumer, colonization of animals in herds or flocks allows easier transmission plus the different sources of primary contamination in the animal farms poses difficulty in bacteriophage implementations. Obviously, both pre- and post-harvest interventions have their advantages and drawbacks, but both strategies should be adapted in order to provide safer food supplies.

Currently, several phage-based products have been approved by EPA, USDA and FDA. ListShield™ (LMP-102) was one of the first phage-based products developed by Intralytic Inc. for food safety and was approved by FDA as a phage cocktail that designed to control *L. monocytogenes* in RTE foods [86]. This phage cocktail also obtained the generally recognized as safe (GRAS) status from FDA. Intralytic Inc. also introduced EcoShield™, which received the FDA clearance in 2011, against *E. coli* O157:H7 contamination on ground meats. Meanwhile, SalmoFresh™, which is specific for *S. enterica* in foods, is the third food safety product that received a GRAS designation for Intralyic Inc. [87]. In 2011, Listex P100 was another anti-*Listeria* phage preparation developed by Micreos Food Safety, the Netherlands, which has received the USDA approval in aiding the removal of *L. monocytogenes* from all susceptible food products. In December 2013, the Micreos Food Safety announced that Salmonelex™ has been approved as a GRAS that against *Salmonella*.

Potential advantages and drawbacks of phage therapy

Advantages of phage therapy: Bacteriophages have a number of desirable properties that make them compelling candidates to be used as biocontrol agents in food as compared to antibiotics and current decontamination approaches in food safety. First and foremost is the mechanisms of action of phage lysis as in generally bacteria that have been infected by the lytic phages are unable to regain their viability. Unlike certain antibiotics, which are bacteriostatic such as tetracycline, allow bacterial evolution towards resistance [88]. The high specificity toward the host pathogenic bacteria strains is the next advantage of the application of lytic bacteriophage. As they do not affect or alter the gut microbiota and nor they change the organoleptic properties of the food products [89]. In contrast, some of the broader spectrum antibiotics tend to induce superinfection such as *Clostridium difficile* colitis [90]. Moreover, the conventional decontamination techniques employed in the food-processing facilities such as chemicals, physical disrupting agents and irradiation have significant drawbacks. As they usually cause corrosion of the instruments used in food processing, damages on foods and also the toxic effects of chemical residues [23]. These deleterious effects are not seen in bacteriophages which are non-toxic and do not interfere with mammalian cells [91]. Furthermore, owing to its abundance and ubiquitous nature of bacteriophages, phages that against the major pathogenic bacteria are readily discovered and isolated especially from sewage and waste materials which contain high bacterial concentration, hence aid in lowering the cost of production [92]. The remarkable stability of phages in food is another valuable properties with some of the bacteriophages able to withstand heat up to 60^{O}C, freezing condition, high osmotic pressure and also a pH of 4.0 [93]. They are also considered to have low environmental impacts as they are consisted of nucleic acids and proteins only with narrow host ranges [94]. Interestingly, some bacteriophages have the ability to disrupt some of the bacterial biofilms [95].

Application of lytic bacteriophages in the improvement of food safety is known to be one of the safest antibacterial approach available now due to theirs highly specificity against the specific bacteria. Furthermore, they are ubiquitous in the environment indicating that human are exposed to them in daily basis. For instance, high numbers of bacteriophages are present on the fresh, fermented and foodstuff that has not been processed extensively. High levels of 10^4 coliphages per gram have been isolated from fresh poultry, meat and raw vegetables [96]. Atterbury et al. [97] isolated *Campylobacter* bacteriophages as high as $4x10^6$ PFU from retail poultry. These evidences showed that human consume vast amounts of phages every day and therefore phages can safely be consumed. Moreover, there is no report regarding the detrimental side effects of phages in humans or animals. Numerous animal studies showed results on the safety of bacteriophages as the biocontrol agents [83,98]. Kang et al. [98] observed no effects on the physical appearance and behavior of the 8 male BALB/c mice in the oral toxicity test after a high titer ($1.1x10^{11}$ PFU/kg body weight) wksI3 phage administered orally. Carlton et al. [83] also demonstrated that no abnormal physical or behavioral changes observed in albino rats which administrated orally with repeated high dose of phage P100 for 5 consecutive days. Convincing evidence shown by a study which involved oral administration of *Escherichia coli* Phage T4 into human volunteers [92]. They found out that neither the low (10^3PFU/mL) nor the high (10^5PFU/mL) phage dosage resulted in any adverse effects [92]. These evidences suggested that the intake of phage with food is safe and it can be used as an additive for bio-preservation of foods.

Drawbacks of phage therapy: Despite all the advantages stated above, one of the major drawbacks of the phage therapy which receive most of the concern is the potential emergence of phage-resistant bacteria mutants, as in the case of antibiotics, and it has been observed in foodborne pathogen and spoilage bacteria [99,100]. Typically, the resistance developed towards a particular phage when the bacteria surface protein is lost and prevents the phage from infecting its host due to the absence of the receptor for attachment. Furthermore, phage resistance can also be achieved through mutation in genes which is essential for phage replication or assembly [101]. The horizontal acquisition of a restriction enzyme system which allows the bacteria to degrade foreign DNA with endonucleases is another route of acquiring the resistance towards phage in bacteria [102]. However, phages are evolving constantly and have the ability to overcome this resistance and the use of cocktails of phages help in resolving the issues of bacterial resistance [103]. Moreover, bacteriophages can induce immune response as they are viruses which are recognized as foreign invaders and are rapidly eliminated from the systemic circulation by reticulo-endothelial system clearance [104], therefore affecting the efficacy of the phage applications. Furthermore, reduced efficacy of bacteriophages has been observed in several studies on the phage treatment for pathogens that colonized the farm animals and also on the surface of food products. It has been suggested that the decreased efficacy of the bacteriophage in the livestock may be due to the exposure to the constantly changing microenvironments and also the interaction with the immune system observed in a living animal [105]. The various components in a food matrix such as carbohydrates, proteins and fats also have slight effects on the ability of the bacteriophage to interact with its specific pathogens [105]. Approaches such as simultaneous administration of antacid and proper encapsulation of phage have been attempted to improve the efficacy of phage treatment [13].

Conclusion and Future Perspective

Majority of the studies demonstrated that phage therapy has the potential to become the main approach in reducing the foodborne pathogens in the food producing animals and also in fresh and processed foods. However, there are still many questions to be addressed such as to further understand the phage-bacteria interactions, the efficacy and pharmacokinetics of the phage treatment, and the phage resistance issue. Furthermore, more *in vivo* studies with appropriate models and complete genome analysis are required to assess the efficacy and safety of the phage. In addition, market acceptance can be a challenge for the use of bacteriophage in a broader basis for biocontrol of foodborne pathogens in foods [23]. The cost of phage production that causes the increased in foods price may not be welcome by the producers and consumers. Moreover, public also may not be able to accept the idea that phages are sprayed on the foods they consume. Hence, education campaign about the safety and advantages of phage-based biocontrol approach could be implemented to educate the public. Some of phages are already commercially available (e.g. ListShield™, EcoShield™ and SalmoFresh™) and approved by FDA [106], thus providing evidence on the safety of phages to be applied not only in food but also in animals and humans.

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