10.21608/AVMJ.2025.364580.1609 Assiut University web-site: www.aun.edu.eg

CAMPYLOBACTER PHAGES: BIODIVERSITY AND APPLICATIONS

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Received: 9 April 2025; **Accepted:** ٤ May 2025

ABSTRACT

Bacteriophages, or phages, are bacterial invading viruses and considered the biosphere's most prevalent biological agents. They reproduce either through a lytic cycle, leading to the lysis of bacterial cells, or a lysogenic cycle by integrating the phage genome into the host genome (temperate phages). *Campylobacter* (*C.*) species, particularly *C. jejuni* and *C. coli*, are the main cause of "Campylobacteriosis," a common form of bacterial gastroenteritis worldwide. *Campylobacter* phages exhibit remarkable biodiversity with significant genetic and morphological variations. Most *Campylobacter* phages are categorized under the *Myoviridae* family, while some belong to the *Siphoviridae* family. Most reported *Campylobacter* phages infect *C. jejuni* and *C. coli* and are lytic phages. This review gives an overview of the biology and classification of *Campylobacter* phages (lytic and temperate), the application of lytic *Campylobacter* phages as antibacterial agents to reduce *Campylobacter* bacteria in the livestock and food industry, and the use of phage typing as a tool for the identification of *Campylobacter* bacteria.

Keywords: Bacteriophages, Phages, Prophages, *Campylobacter jejuni*, *C. coli*.

INTRODUCTION

1. Bacteriophage and life cycle

Bacteriophages are viruses that attack and proliferate within bacterial cells, ultimately liberated by lysing the host cell (Marcó *et al.,* 2012). Hankin observed in 1896 that water from Indian rivers contained substances capable of destroying a wide variety of bacteria, and could pass through bacterial porcelain filters but lost their antibacterial activity when heated to boiling temperatures. (Waldor & Friedman, 2005). Bacteriophages were identified independently by Frederick Twort in 1915 and Félix d'Herelle two years later, as agents that lyse bacterial cells in liquid cultures and produce clear zones (plaques) on agar surfaces. D'Herelle noted that these microorganisms infiltrated bacterial hosts, replicated within them, and triggered cell rupture. D'Herelle called them "bacteriophages" (Abedon, 2008; Ceyssens, 2009). Phages are extensively disbursed on the planet and are present in all environments where bacteria exist (Clokie *et al.,* 2011; Dion *et al.,* 2020). Bacteriophages have a significant impact on gene transfer, microbial ecology, and the evolution of bacterial genomes due to their widespread distribution and abundance (>10^{31}) (Ohnishi

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et al., 2002; Piña-González *et al.,* 2024). The phage particles are typically made up of linear or circular nucleic acid, which can be single-stranded DNA, double-stranded DNA, single-stranded RNA, or double-stranded RNA, with an outer protein coat surrounding it. Based on their morphology and nucleic acid content, the International Committee on Taxonomy of Viruses (ICTV) categorized bacteriophages into various orders. The order *Caudovirales* includes phages with a tail and double-stranded DNA (**Fig. 1**). It consists of three families: *Siphoviridae, Myoviridae,* and *Podoviridae*. The majority of published phages belong to the order *Caudovirales*. Bacteriophages typically target only closely related strains and are highly host-specific.

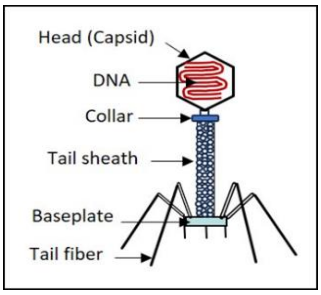

Fig. 1: Structure of a bacteriophage

Phage adsorption is the first step of phage infection, where the bacteriophage binds to the phage receptors on the host cell using the receptor binding protein, which is found on the baseplate of the phage tail, then followed by the injection of phage DNA (Abedon, 2020; Leiman *et al.,* 2003). There are two life cycles for phages: lytic and lysogenic (**Fig. 2**). In the lytic cycle, the injected phage genome replicates and multiplies, causing lysis of cells and production of newly assembled phages. Phages that undergo this cycle are called lytic or virulent phages. During the lysogenic cycle, the injected phage DNA integrates with the bacterial chromosome and is transferred to the new cells during cell division. Bacteria that carry the integrated phage-genome are known as "lysogens", and the integrated DNA is called a "prophage". The prophage can either spontaneously enter the lysis cycle or be induced by Mitomycin C or ultraviolet (UV); the resulting phages are named "temperate" phages.

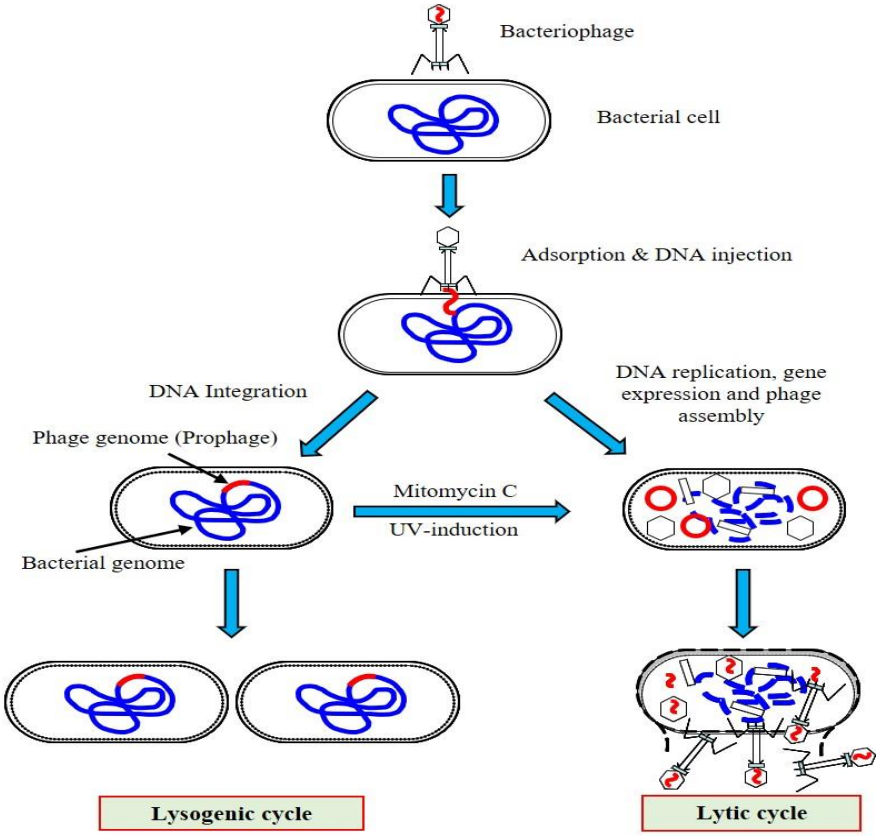

Fig. 2: Life cycles of bacteriophages

The most prominent temperate phage is the bacteriophage lambda (λ), which infects *Escherichia coli*. It has a double-stranded genome size of 48.5 kbin length. Phage lambda has been considered a fundamental tool in molecular biology and genetic engineering research (Casjens & Hendrix, 2015; Chatterjee & Rothenberg, 2012).

2. Bacteriophage propagation, concentration, and purification

Phage propagation is usually carried out either by propagating lytic phages (on double-layer agar plates or in liquid media) or by inducing lysogenic strains (in the case of temperate phages) using Mitomycin C or UV. For small volumes (10-50 ml), after complete lysis of the liquid bacterial culture and SM buffer (Sodium chloride-Magnesium sulphate buffer) obtained from washing agar plates with confluent lysis, the cell debris is removed directly by filtration via a syringe filter with 0.45 and 0.22 µm pore size, or after centrifugation at 10,000 × g for 20 min. (Jäckel *et al.,* 2019). For large volumes and for getting highly purified phages, an isolation protocol using Cesium Chloride (CsCl) gradient centrifugation (Ali, 2009; Sambrook *et al.,* 1989) can be used. As presented in **Fig. 3**, after cooling the lysed bacterial culture (1 liter) to room temperature, deoxyribonuclease and ribonuclease are added for the degradation of bacterial nucleic acids. The mixture is maintained at room temperature for one hour. Subsequently, sodium chloride is supplemented to obtain a one-molar solution, mixed gently, and the lysate is chilled on ice for one hour. Centrifugation is used to separate the cellular debris, and the supernatant is then moved to a new bottle. Polyethylene glycol (PEG 6000) is incorporated at 10% (weight/volume), mixed, and chilled on ice for ≥1 hour. PEG-Phages were pelleted by centrifugation, the supernatant is removed, and the remaining sediment is left to air dry by inverting the centrifuge bottle for a few minutes. The pellet is suspended in 15 ml of SM buffer using gentle agitation either via a wide-pore pipette or by rolling/swirling the bottle for ten to fifteen minutes. CsCl solutions of different densities in SM buffer are prepared and layered into polypropylene centrifuge tubes, beginning with the densest solution at the bottom**.** Finally, the phage-containing SM buffer is layered atop the gradient, followed by ultracentrifugation. Post-centrifugation, a distinct bluish phage band is obtained. This band is cautiously extracted using a syringe. The purified phages are kept in a refrigerator for downstream uses, such as phage DNA isolation, electron microscopy, antibody production, or protein profiling.

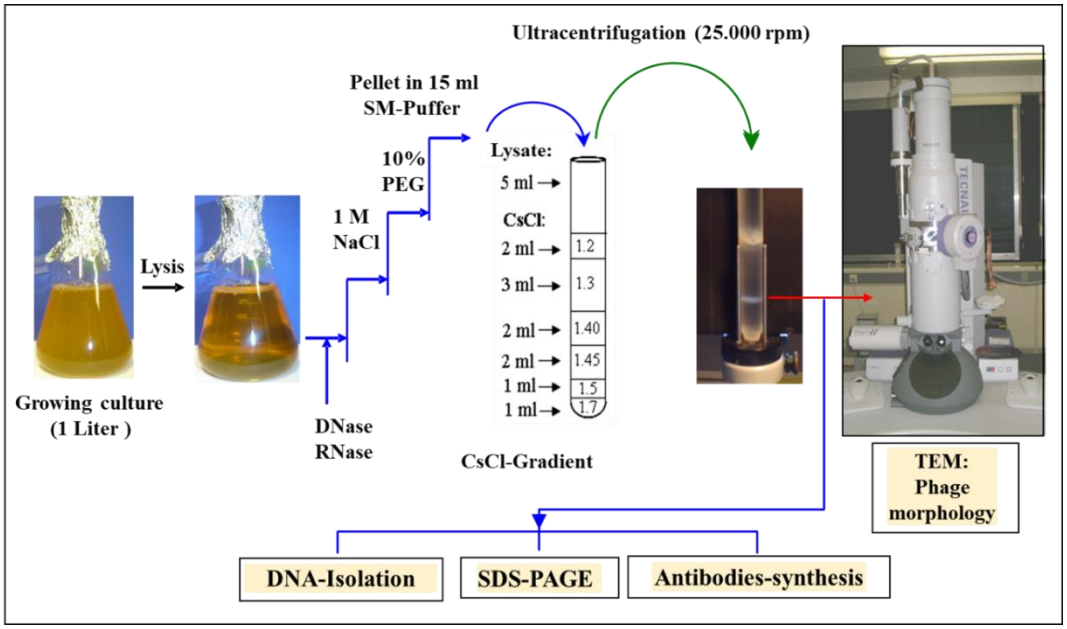

Fig. 3: Diagram of phage isolation protocol using CsCl gradient centrifugation

CAMPYLOBACTER SPP.

The genus *Campylobacter* (*C.*) includes thirty-two species and nine subspecies and belongs to the family Campylobacteraceae (Costa & Iraola, 2019). *Campylobacter* bacteria are Gram-negative, spiral-shaped rods (Gull wings) or curved, measuring 0.2–0.8 μm in width and 0.5–5.0 μm in length. A single, polar flagellum is present on one or both ends of the *Campylobacter* bacterium and is responsible for the corkscrew-like movement (Facciolà *et al.,* 2017; Nachamkin *et al.,* 2008). Under microaerobic conditions (5% O_2, 10% CO_2, and 85% N_2), *Campylobacter* bacteria thrive optimally at temperatures between 37°C and 42°C. When exposed to stressful environments, the bacteria can adopt spherical or coccoid morphologies, transitioning into a "viable but non-culturable state" (Tholozan *et al.,* 1999). *Campylobacter* bacteria should be cultured in flasks instead of tubes, because large surfaces for gas exchange enhance their growth. Different media can be used to cultivate *Campylobacter*, such as Mueller-Hinton, Brain Heart Infusion, and Brucella broth (Jäckel *et al.,* 2019). *Campylobacter* bacteria are found everywhere in environment (Champion *et al.,* 2005; Maugeri *et al.,* 2004). *Campylobacter* bacteria constitute a fraction of the normal flora in the digestive system of birds and other animals. The food borne illness “Campylobacteriosis”, a globally prevalent type of bacterial gastroenteritis, is caused primarily by *C. jejuni and C. coli* (Guerry, 2007; Sahin *et al.,* 2017). Poultry has been identified as the principal reservoir of *Campylobacter* infections, mainly via handling and consumption of inadequately cooked meats (Authority *et al.,* 2018; Belanger & Shryock, 2007; Shane, 2000).

CAMPYLOBACTER BACTERIOPHAGES

1. Virulent *Campylobacter* phages

So far, the most reported *Campylobacter* phages infect mainly *C. jejuni* and *C. coli;* they are lytic (virulent) and members of the *Myoviridae* family, i.e., with contractile tails (Javed *et al.,* 2014; Sørensen *et al.,* 2021; Ushanov *et al.,* 2020). A few *Siphoviridae* phages (with non-contractile tails) infecting *Campylobacter* have been reported, but little information is available (Atterbury *et al.,* 2003; Hwang *et al.,* 2009; Sails *et al.,* 1998; Ushanov *et al.,* 2020). According to their morphology and size of genomes, lytic *Campylobacter* phages have been categorized into three groups (**Table 1**). Phages of group I have larger head dimensions than phages of the other groups, large genomes (320 - 425 kb), and are rare in number (El-Shibiny *et al.,* 2009; Sails *et al.,* 1998). In addition, no genome sequences are available in the gene bank for group I *Campylobacter* phages. Members of Group II (175 - 183 kb) and Group III (131 - 135 kb) have been highly isolated in many countries (Javed *et al.,* 2014; Sails *et al.,* 1998). Group II and III phages exhibited a limited burst size, exceptionally low GC content (26–27%), and resistance to cleavage by numerous DNA restriction enzymes (Carvalho *et al.,* 2010; Hammerl *et al.,* 2014; Lis & Connerton, 2016). An explanation for this observation is that these phages have an evolutionary response to the restriction-modification systems in host strains, or that the phage DNA may carry one or more methyltransferase genes that change the recognition site of one or more DNA restriction enzymes. Based on the National Center for Biotechnology Information (NCBI) database, there are 11 families and 11 genera of *Campylobacter* phages (Piña-González *et al.,* 2024). However, only three phages were categorized under group II (CP21, CPt10, and CP220) (Hammerl *et al.,* 2012; Timms *et al.,* 2010) and eight phages belongs to group III (CP81, CP30A, NCTC12673, PC14, PC5, vB_CjeM_Los1, CPX (NC_016562), and CP8) have been completely sequenced (Janež *et al.,* 2016; Kropinski *et al.,* 2011; O’Sullivan *et al.,* 2018), whereas the genome of group II phage vB_CcoM-IBB_35 has been partially sequenced (Carvalho *et al.,* 2012). Genome analysis within each group revealed high similarities. In contrast, only weak homologies were observed between the phage genomes of groups II and III. Consequently, two new genera,

Firehammervirus (former names = Cp220likevirus and CP220virus) and Fletchervirus (former names = Cp8unalikevirus and CP8virus), respectively, have been developed (Adams *et al.,* 2016; Javed *et al.,* 2014; Sørensen *et al.,* 2021; Sørensen *et al.,* 2015). Moreover, the genome of group II phages harbors large modules interrupted by long DNA repeats, which might result in rearrangement of the genome, meanwhile group III phages possess collinear genomes (Javed *et al.,* 2014). The genomes of both groups showed resistance to many restriction enzymes (Ushanov *et al.,* 2020). Furthermore, Zampara *et al.* (2017) reported that *Campylobacter jejuni* group III phages adsorb to *Campylobacter jejuni* using capsular polysaccharide (CPS) receptors, while group II phages adsorb to the sensitive bacteria via flagella. Thus far, PCR and sequencing have identified two subgroups of group II phages exhibiting a different modular genome organization and host range (Hammerl *et al.,* 2012; Jäckel *et al.,* 2015). Group II phages infect both *C. jejuni* and *C. coli* (Sails *et al.,* 1998), while phages of group III often lyse more *C. jejuni* strains than group II phages and may show more lytic activity (Jäckel *et al.,* 2015; Timms *et al.,* 2010). More recently, a new Campylobacter phage, CP6, was isolated from chicken feces using the MDR (multi-drug resistant) Campylobacter Cc512 as a host strain. Morphologically, the CP6 phage showed an icosahedral head (80.53 ± 1.02 nm in diameter) and a short, non-contractile tail (94.35 ± 1.05 nm). It has a linear DNA of 178,350 bp in length, with 27.51% total GC content, and is thus classified as a member of group II *Campylobacter* phages. Moreover, genome analysis of the phage CP6 revealed high similarity to *Campylobacter* phage CPt10, CP21, CP20, IBB35, and CP220 (Zhang *et al.,* 2024).

Table 1: Classification of lytic *Campylobacter* Phages

Size of Phage genome (kb)	Group	Group's Name	Phage receptors
320 – 425	I	-	Flagella
175 – 183	II	Firehammervirus (Cp220likevirus & CP220virus)	Flagella
131 – 135	III	Fletchervirus (Cp8unalikevirus & CP8virus)	Capsular Polysaccharide (CPS)

2. Temperate *Campylobacter* phages

Like other bacteria, *Campylobacter* spp. can harbor prophages or prophage remnants. (Clark & Ng, 2008; Scott *et al.,* 2007). Temperate phages were first reported from *Campylobacter fetus* (old name *Vibrio fetus*) in 1968 after induction with Mitomycin C (Firehammer & Border, 1968). After that, twenty-two *Campylobacter* phages were induced from lysogenic *C. fetus* (old name *Vibrio fetus*) and isolated, and one phage, the phage V-45, was characterized. Morphologically, the phage V-45 has a non-contractile tail of 240 nm in length and an isometric head of 50 nm in diameter (Bryner *et al.,* 1970). Fouts *et al.* (2005) identified three *C. jejuni*-integrated elements (CJIE) in *C. jejuni* strain RM1221: CJIE1, CJIE2, and CJIE4. CJIE1 is a Mitomycin C-inducible *Campylobacter* Mu-like phage (CMLP1/ CampMu-like phage 1). CJIE2 and CJIE4 are similar prophages, and their genome encodes a few structural proteins. CJIE3 has been reported and indicated as an integrative plasmid (Fouts *et al.,* 2005). A few years later, a new integrated element called CJIE5 prophage was described (Skarp *et al.,* 2015). Recently, the bacteriophage DA10 is the only *Campylobacter* phage reported as an excised temperate phage (Hooton *et al.,* 2020). The phage DA10 was

first isolated from poultry samples and morphologically characterized by Aprea *et al.* (2018). Morphologically, DA10 showed an icosahedral head (67 ± 3.7 nm), a neck-like structure, and a contractile tail (93.5 ± 3.7 nm in length and 21.6 ± 3.0 nm in diameter), and thus was classified as a member of the *Myoviridae* family. Consequently, the DA10 phage heads are smaller and tails are shorter than previously reported virulent *Campylobacter* II/III phages (heads: 92–96 nm and tails: 115–148 nm), considering DA10 as a new class of *Campylobacter* phage. Hooton *et al.* (2020) reported that the phage DA10 has the shortest genome (35,379 bp) compared to other recorded *Campylobacter* phage genomes in GenBank. It represents a novel excised prophage in the genome of *C. jejuni* CJ677CC520 (36,401 bp). It can infect a set of *C. jejuni* and *C. coli*. DA10-like prophage sequences were found in rare numbers of *C. jejuni* and *C. coli,* and six with complete genomes were identified with genome sizes of about 33 to 38 Kb. This rarity may be attributed to the presence of about 30 bp spacer sequences of *Campylobacter* Type II-C CRISPR arrays in 75% of the ORFs of DA10, which are associated with mediated immunity. More recently, Piña-González *et al.* (2024) investigated the integrated prophages in 446 high-quality and complete genomes of *Campylobacter* species isolated from different sources and revealed 431 prophages harboring these species.

CAMPYLOBACTER PHAGE THERAPY

Unlike broad-spectrum antibiotics, phages typically show high selectivity. Many phages are specific to a single bacterial species, or even specific to only a few strains within that species (Koskella & Meaden, 2013; Lin *et al.,* 2017). To assess the effectiveness of *Campylobacter* phage therapy, broilers were experimentally colonized by *C. jejuni* isolates HPC5 and GIIC8 from United Kingdom broiler flocks (Loc Carrillo *et al.,* 2005). Fifty-three *Campylobacter* phages were screened against 130 *Campylobacter* isolates (50 isolates from broiler chickens and 80 strains isolated from humans). After the screening, two lytic phages (CP8 and CP34) with a broad host spectrum were isolated. The phages, CP8 and CP34, were given orally to 25-day-old broilers experimentally infected with the *C. jejuni* isolates in antacid suspension at various dosages. Compared to untreated controls, *Campylobacter* counts decreased between 0.5 and 5 log10 CFU/g of cecal samples in treated birds with *Campylobacter* phages over five days after treatment. Another experiment was conducted to test a phage cocktail of three phages (phiCcoIBB35, phiCcoIBB37, phiCcoIBB12) to control broiler birds infected with *C. jejuni* and *C. coli.* (Carvalho *et al.,* 2010). Phage administration was carried out through two routes (oral gavage and in-feed). After phage administration, birds showed no signs of disease, even at the highest dose of *Campylobacter*. The phage cocktail reduced the titter of both *C. jejuni* and *C. coli* in feces by about 2 log10 CFU/g when administered by oral gavage and in feed. This decline remained consistent throughout the experiment, with neither pathogen recovering its original population. The decrease in *Campylobacter* titer was observed earlier when the phage cocktail was mixed with the birds' feed, than when it was administered by oral route. About 13% of *Campylobacter* strains resistant to phage infection were observed in phage-treated chickens. Another study tested *Campylobacter* reduction using a phage cocktail on three commercial broiler farms (Kittler et al. (2013). Hammerl *et al.* (2014) compared the lytic properties of one group II and two group III phages and analyzed the effect of phage application on reducing *C. jejuni* counts in broiler chickens. The *Campylobacter* phages were administered to three groups of chickens in different combinations, each consisting of ten birds. Results showed that group III phage CP14 reduced *Campylobacter* bacteria by more than 1 log10 unit. The administration of CP81 phage (a second group III phage) showed no reduction, probably due to the developed phage resistance. The second group of chickens was administered with phage CP14,

and 24 hours later, the phage CP68 (group II phage) reduced the *Campylobacter* counts by more than 3 log10 units. So, successive application of group III and group II phages reduced the numbers of *C. jejuni* in chickens most efficiently (Hammerl *et al.,* 2014). Therefore, selecting well-characterized *Campylobacter* phages with a broad host range could be available to reduce *Campylobacter* infections in animals and food products. Recently, the new *Campylobacter* phage CP6 was isolated from chicken feces using the multidrug-resistant (MDR) *Campylobacter* Cc512. (Zhang *et al.,* 2024). The phage CP6 revealed a broad host range (97%) against thirty-five MDR *Campylobacter* isolates. As a result, it was isolated and characterized as an alternative effective tool to prevent and control *Campylobacter* in chicken.

PHAGE TYPING OF *CAMPYLOBACTER* SPP.

Phage typing could be used in addition to serotyping to provide more reliable identification of *C. jejuni* and *C. coli* (Frost *et al.,* 1999). Phage typing was performed using 2407 *C. jejuni* and 182 *C. coli* strains obtained during the period from 1996 to 1997. Fifty-seven *C. jejuni* phage types were detected in 60% of examined isolates. PT1 was the most prevalent phage type (20% of samples). Meanwhile, PT2 and PT7 discovered 12 phage types identified in *C. coli* isolates (75.2% of the analyzed isolates). It was concluded that the typing of *C. jejuni* and *C. coli* is enhanced by combining phage typing and serotyping, which allows for even more differentiation.

CONCLUSION

Phages of *C. jejuni* and *C. coli* are the most reported and studied *Campylobacter* phages, and they are lytic phages. *Campylobacter* bacteria are one of the food born pathogens that can be controlled along the food chain by applying lytic phages as antibacterial agents, which is called phage therapy. For efficient and powerful phage therapy, phage cocktails of lytic *Campylobacter* phages group II and III, with a broad host range, should be selected. *Campylobacter* phages could represent a promising tool for controlling *Campylobacter* infections in poultry farms and the food industry. The specificity and ability of bacteriophages to target antibiotic-resistant strains make them an attractive alternative to traditional antimicrobials. However, challenges such as host range limitations, development of phage resistance, and regulatory barriers must be addressed to overcome. Optimizing phage therapy strategies for food safety and public health requires ongoing research and innovation, particularly in the biology and ecology of *Campylobacter* phages and their interactions with *Campylobacter* bacteria.

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فاجات الكامبيلوباكتر: التنوع البيولوجي والتطبيقات

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العاثيات (لاقمات البكتيريا أو البكتيريوفاجات) ، أو الفاجات، هي فيروسات تصيب البكتيريا، وتُعتبر أكثر العوامل البيولوجية انتشارًا في المحيط الحيوي. تتكاثر إما من خلال دورة تحللية، مما يؤدي إلى تحلل الخلايا البكتيرية، أو دورة إندماجية عن طريق دمج جينوم العاثية في جينوم العائل (العاثيات المعتدلة أو الكامنة). تُعدّ أنواع الكامبيلوباكتر (العطيفة) وخاصةً العطيفة الصائمية (*C. jejuni*)، والعطيفة القولونية (*C. coli*) من نوع العاثيات المحللة, هما المسبب الرئيسي لمرض "الكامبيلوباكتيريوزس"، وهو شكل شائع من التهاب المعدة والأمعاء البكتيري في جميع أنحاء العالم. تتميز عاثيات كامبيلوباكتر بتنوع بيولوجي ملحوظ مع اختلافات جينية ومورفولوجية كبيرة. تُصنف معظم عاثيات كامبيلوباكتر ضمن عائلة ميوفيريدي (Myoviridae)، بينما ينتمي بعضها إلى عائلة سيفوفيريدي (Siphoviridae).

تُقدّم هذه المقالة لمحةً عامة عن بيولوجيا وتصنيف عاثيات الكامبيلوباكتر (التحللية والمعتدلة)، واستخدام عاثيات كامبيلوباكتر التحللية كعوامل مضادة للبكتيريا للحد من بكتيريا كامبيلوباكتر في قطاعي الثروة الحيوانية والأغذية، واستخدام تصنيف العاثيات كأداة لتحديد بكتيريا كامبيلوباكتر والتعرف عليها.

الكلمات المفتاحية: العاثيات (لاقمات البكتيريا أو البكتيريوفاجات)، الفاجات، الفاجات الأولية (Prophages)، العطيفة الصائمية (*C. jejuni*)، العطيفة القولونية (*C. coli*).