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Review Article

Impact of supplementation of bacteriophages in poultry production

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Abstract

The growing worldwide demand for animal protein, fueled by population expansion, urbanization, and rising incomes, has hastened the transition from vast to intensive poultry farming methods. While intensive systems provide great production and economic benefits, their dependence on antibiotics to stimulate growth and prevent sickness has led to the worrisome emergence of antimicrobial resistance. The rise of multidrug-resistant bacteria, as well as antibiotic residues in chicken products, pose severe public health threats. In light of mounting worries about antibiotic abuse, bacteriophages - viruses that particularly target bacteria - have returned as a possible, natural alternative to antibiotics in chicken production. Bacteriophages have robust, highly specific bactericidal effects, as demonstrated by investigations on common poultry diseases such as *Salmonella* spp., *Escherichia coli*, *Campylobacter* spp., and *Clostridium perfringens*. Beyond disease management, phage treatment has been found to improve chicken growth performance, intestinal health, and nutrient absorption. This paper examines the mechanism of bacteriophage activity, their use in chicken feeding, and their role in lowering antibiotic dependency, providing a long-term path ahead for safe poultry production and improved global food security.

Keywords: Anti microbial resistance, Antibiotics, Bacteriophage, Intensive farming, Poultry

Highlights

- Intensive poultry farming drives antibiotic use, contributing to antimicrobial resistance
- Bacteriophages offer a natural, targeted alternative to antibiotics in poultry production
- Phages effectively control major poultry pathogens: *Salmonella*, *E. coli*, *Campylobacter*, and *C. perfringens*
- Phage therapy improves gut health, nutrient absorption, and growth performance in broilers
- Adoption of phage-based strategies supports sustainable poultry farming and food safety

INTRODUCTION

With the increase in the world's population, income, and modernization, there has been an unmatched growth in demand for animal protein that is found in eggs, meat, milk, etc. Thereby animal husbandry especially poultry started transitioning from an extensive system of rearing to an intensive farming system (Hedman et al., 2020). Intensive poultry farming being required with less capital, less space, high returns in a limited period with simple marketing is highly beneficial for the farmers and also led to fast per capita to them (Dibner & Richards, 2005). A group of domesticated birds that are reared for animal products (meat, egg, manure), fibre (feathers), and entertainment (fighting, racing) are called poultry. Poultry husbandry is defined as a household and a small-scale production system that make up the major part of chicken production. It is done in rural, peri-urban, and urban areas (Alders & Pym, 2009). The chicken itself comprises 90% of poultry production globally. Global poultry meat consumption is estimated to be 17.2 kg per capita income in 2030.

In an intensive farming system, farmers are allowed to use anti-microbials as growth promoters in the prevention of disease for quick growth, to increase the feed assimilation rate, and to decrease the mortality rate caused by the lethal pathogens (Leener et al., 2005). An anti-microbial agent is a substance that occurs naturally, synthetic or semi synthetically that inhibits the growth or kills the bacteria by exhibiting anti-microbial properties at their respective concentrations (World Health Organization, 2015).

Anti-microbials are effective against the virus, bacteria, protozoa and fungi but antibiotics bacterials play a major role regarding public health. Antibiotics in poultry are administered at therapeutic doses (for

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treatment purposes), metaphylaxis (to prevent the disease) and growth promoters (Poole et al., 2013). Antibiotics like oxytetracycline, bacitracin, chlortetracycline, tylosin, neomycin, avoparin and virginiamycin are generally added to treat intestinal diseases like colibacillosis, necrotic enteritis and other diseases which are the main reasons(affections) for major economic losses in the poultry industry.

The prolonged use of antibiotics at subtherapeutic doses alter the gut microbiome of the bird by colonizing the gut microbiome (Hershberger et al., 2005). Poultry excreta which are said to be a major part of the poultry waste may have this anti-microbial resistant bacteria and animal originated bacteria (Roth et al., 2019). Thereby, they are shed directly into the soil, this enters into plants, animals, humans via the food chain. This causes a decreased efficiency of antibiotics to treat the infected individuals and is solely responsible for anti-microbial resistance for human pathogens i.e., genes responsible for anti-microbial resistance have been transferred from animal to human microbiome. Few studies have revealed that antibiotic residues are present in food animal products like chicken meat and milk which is a global concern at present. The intensive farming system is not only associated with anti-microbial resistance in animals and humans but also with the threat of H5N1 (highly pathogenic avian influenza) and Porcine respiratory syndrome. It was said that intensively reared poultry are the animal reservoirs of multidrug resistance (Chung et al., 1997). The average annual consumption of anti-microbials per kilogram of animal produced globally is estimated to be 45 mg/kg, 148 mg/kg, and 172 mg/kg for cattle, chicken, and pigs respectively. It is estimated that between 2010 & 2030 global consumption of antimicrobials may increase by 67%, from 63,151±1560 tonnes to 1,05,596±3,605 tonnes. Studies revealed that antibiotic consumption in animals is twice when compared to humans. In 2010, the list of top 5 countries in antimicrobial consumption in food animal production were China (23%). USA (13%), Brazil (9%), India (3%), Germany (3%). By 2030, this might scale up *viz.* China (30%), USA (10%), Brazil (8%), India (4%), Mexico (2%)(Van Boeckel, 2015). The highest bacterial disease burden in the world is in India. India has no regulations on the use of antibiotics as antimicrobials in cattle, chicken, pigs (Maron et al., 2013). Till now, there is no quantitative data for the use of antibiotics in poultry as it is poorly targeted and critically understudied. Developed countries like Sweden, Denmark, Norway, and E. U are prohibiting antibiotic use in the poultry industry (Muaz et al., 2018). With the knowledge of antibiotic resistance, multidrug-resistant bacteria, animal originated bacteria, consumer preference has been shifting to "No Antibiotics Ever" or "Raised Without Antibiotics". Therefore, in the past two decades, a huge level of research has been focussing on alternative strategies for antimicrobials that would maintain the animal production, performance and reduce the delitarious effects of antibiotic use in poultry feeding. This review, therefore, focuses to fill the gap of knowledge and provides a basic overview of Bacteriophages, an alternative strategy with its efficacy and mechanism of action that could be employed to improve the performance of the poultry. It has been a novel alternative that has similar beneficial effects to an antibiotic in terms of production performance and nutrient availability.

Bacteriophages

Bacteriophages (phages) are defined as viruses that attack bacteria specifically. They are one of the most fearsome killing machines that are adverse and an abundant biological entity on the earth (Gómez, 2011). Bacteriophages stick to the prey with their leg like fibres which trigger their shaft to insert their genome into the bacteria. Fedricktwort and Felix d'Herelle discovered the bacteriophages independently. Their use as anti-microbials was practised way back in the 1920s but due to rapid growth in the success of practising antibiotic use in the treatment of diseases across the world, the use of bacteriophage has been reduced. Some countries in Eastern Union and the Soviet Union continued the Bacteriophage use as anti-microbial, which is also called phage therapy, but abandoned in the West (Citorik et al., 2014).

Bacteriophage - antimicrobial property: Bacteriophages which are characterized mostly, are dsDNA tailed phages. They are members of *Caudovirales*. Phages are differentiated into two types based on their lifecycle. Phages that enter the lytic cycle are virulent and those which can enter into lytic/lysogenic cycles are temperate phages. The targeted bacteria have specific cell surface receptors, which will get attached by phages irreversibly, with their leg like fibres, dispatches the envelope and injects the genomic material contained within the head into the bacterium. The host (bacterium) provides the required machinery for the replication of the phage genome leading to the production of proteins that are essential for new virions assembly. During the late stages of the lytic cycle, phage-encoded holins and

lysins are expressed. These are responsible for the lysis of bacterial cell walls and release the viral progeny. In this case, virulent phages replicate quickly and cause the lysis of bacterial cells. These kinds of virulent phages are used in bacteriolytic based therapeutics.

Unlike virulent phages, temperate phages enter the lysogenic cycle which does not cause phage production immediately. Instead, they form a prophage, that is either through the integration of bacteriophage genome with bacterial DNA genome or through the formation of extrachromosomalplasmid (Dy et al., 2018). This newly formed prophage replicates along with the bacterial genome for many generations when the favourable conditions (stress) get arrived, then the newly formed prophages in temperate cycle shifts to lytic cycle.

Phages and their products are used as antimicrobials in multiple ways. The narrow spectrum antimicrobial property of bacteriophages which is host specific that kills the bacteria, can be used directly, indirectly (by lytic enzyme utilization) and genetic delivery systems. During the treatment of bacterial diseases, virulent phages are isolated, purified and then administered. Its characteristic feature of host specificity is because of its action on the appropriate hosts exactly leaving unaffected for the non-host cells (Yen et al., 2017). Sometimes, phage resistance can be seen in bacteria when only one type of bacteriophage is used in the treatment (Goodridge et al., 2018). Therefore, cocktails of different virulent phages are used that they identify various bacterial cell surface receptors accordingly (Goodridge et al., 2018).

Phage proteins: The lysins are the phage proteins, which tear down the peptidoglycan layer of the bacterial cell wall. This enables the release of bacteriophage genomic entities into the host cell. In the case of gram-negative bacteria, lysins are added with chemical permeabilizers or peptide sequences that are responsible for the breakdown of bonds in the outer membrane. In the case of gram-positive bacteria, recombinant lysins are used successfully (Fenton et al., 2010).

Non-lytic bacteriophage anti-bacterial property: The virulent phages cause rapid bacterial lysis which results in the formation of various harmful toxic products by the bacteria simultaneously. Therefore, bacteriophages will be genetically engineered so that they could either inhibit the targeted bacterial replication or make them susceptible to antibiotics. Studies revealed that bacteriophage when combined along with antibiotics are also successful (Citorik et al., 2014).

Role of Bacteriophage in poultry feeding

Background: Poultry intensive farming**-** In Intensive farming systems like production systems poultry are reared in large and dense manner that encourages disease transmission because of low genetic diversity (Jones et al., 2013). *Salmonella* spp., *E. coli* spp., *Campylobacter* spp., *Clostridium* spp. and *Listeria* are some of the most common poultry zoonotic bacterial pathogens (Wernicki et al., 2017; Czaplewski et al., 2016). UK Department of Health and the Wellcome Trust has sponsored a review stating that out of 10 most promising alternative strategies, three are of bacteriophages and their components. According to the recent phage therapy studies, the following sections are summarized in poultry feeding:

Salmonellosis**-** Most endothermic animals and human beings are susceptible to infections caused by *Salmonella*. Thereby, *Salmonella* is the major target for phage therapy and that has been a success in various degrees (Miller et al., 2010). To demonstrate the *Salmonella* colonization in the caecum, an experiment was conducted by Sklar, (2001) in which a cocktail of phageswere administered for 14 days broiler chicken feeds, which resulted in a reduction of *Salmonella* colonization in the caecum by almost 1 $\log_{10}$ Colony Forming Unit/g There was also reduced secondary infection, only 3 out of 10 birds when given bacteriophages in their diets showed mild air sacculitis and 8 out of 10 birds of the control group which were not given bacteriophages, showed air sacculitis (Sklar, 2001). Research conducted by Fiorentin et al. (2005) revealed that there is a decrease in the colonization of *Salmonella enteritidis* to 3.5log10 CFU/g in 7-day old chicks which were already challenged with 10^8 CFU of *S. enteritidis*. This resulted when the experimental chicks were administered with a single dose of three bacteriophages each at 10^{11} PFU (Plaque Forming Unit) (Fiorentin et al., 2005). Three lytic phages (different serotypes) have been collected from poultry farms, waste water in the UK by Atterbury et al. (2007). They had a wide host range against *S. enteritidis, S. Hadar* and *S. Typhimurium*. 36-day old Ross broiler birds were fed with the diets treated with) the collected bacteriophages at a concentration of 9.0 $\log_{10}$ PFU each for 6 days . A reduction in *Salmonella* colonization of caecum, out of that *S. enteritidis* and *S. Typhimurium* were reduced significantly. In a study, (Berchieri et al., 1991) treated birds challenged with *S. Typhimurium* with bacteriophages (*S. Typhimurium* strains F98 [phage type 14], Beauville [phage type 40], and 1,116 [(phage type 141)] at a dose of 1012 plaque

forming units (PFUs)/mL. They found that the mortality rate linked to *S. Typhimurium* was possibly reduced to 20% as instead of 56% in the untreated group. However, six hours after treatment, *S. Typhimurium* returned to its pre-treatment levels and was not completely eradicated due to lesser concentrations of phages. Additionally, if *Salmonella* was present, the bacteriophages failed to survive in the digestive tract. Bacteriophages often only survived as long as they were added to feed orally. This limitation can be removed by the use of high titre bacteriophages while feeding (Atterbury et al., 2007) For bacteriophages to be effective, they must be administered in significant quantities and right away following *S. Typhimurium* infection.

Colibacillosis- One of the biggest health risks in the global chicken sector is *Escherichia coli*. Airsacculitis, colisepticemia, coligranuloma, enteritis, omphalitis, orchitis, osteomyelitis, panophthalmitis, peritonitis, salpingitis, septicemia, and swollen-head syndrome are among the severe health issues it produces in animals (Kittler et al., 2020). An experiment was conducted by Huff et al. (2002) in which a high titre of 2 phages (SPR02, 2.6×10^8 PFU/mL and DAF6, 2.35×10^9 PFU/mL) were sprayed on day 7, which was followed by *E. coli* injection directly into the thoracic cavity @ (5.6×10^4 CFU) at day 7, 8, 10. Results revealed that there was a 30% mortality rate in bacteriophage sprayed birds and a 60% mortality rate for untreated control birds (Huff et al., 2002). Oliveira et al. (2010) conducted phage delivery through a fine drop scatter spray in the case of chickens which are injected experimentally and naturally. A twelve 10-week-old Rhode Island Red were injected with 1×10^8 CFU of avian pathogenic *E. coli* H839E, in the left thoracic air sac. Followed by spraying and oral administration of phage @ 1.5×10^9 PFU phi F78E. A reduction in pathology score (2.5), morbidity (60%), mortality (45%) in phage treated group was observedwhile the control group had pathogenic scorewith high morbidity (100%), mortality (75%). An experiment conducted by El-Gohary et al. 2014 in which 200 mL of bacteriophage (2.8×10^8 CFU/mL) was sprayed to pathogenic *E. coli* culture on the surface area of 3.9 m^2 pen. There was a reduction of mortality (5%) in the phage treated and 25% in the control group. Therefore it is suggested that bacteriophage can be used for sanitizing the environment that reduced the concentration of the targeted pathogen to below infectious dose. Phage GN06 significantly inhibited avian pathogenic *E. coli* in both liquid medium and the growth of biofilm, according to Wang et al. (2022). Wild pigeon droppings contain United Arab Emirates MI-01, a bacteriophage with lytic activity against *E. coli* O157: H7, indicating they may carry pathogenic *E. coli* O157:H7 (Sultan-Alolama et al., 2022). Phages flora and kanamycin sulphate (KM18) that target *E. coli* were identified by Jiang et al. (2022). The lytic spectrum of phage flora is broader than that of KM18. Phage flora also showed greater antibiofilm properties compared to kanamycin sulfate in expanded *E. coli* cultures. The combination of phage flora and kanamycin sulfate showed better antibiofilm properties in minimum *E. coli* cultures than either flora or kanamycin sulphate singly.

Campylobacteriosis- A major reason for the acute bacterial food borne diseases in E.U. It has a low infectious dose for humans and can easily get colonized in the Avian gut (European Food Safety Authority, 2018). Oliveira et al. (2010) evaluated that phage preparation when administered by oral gavage has shown its protective effect on adults only when after challenging with *C. jejuni* (10^5 CFU/mL) than on 10-day old Ross Broiler chicks. Carvalho et al. (2010) experimented and revealed that Campylobacter counts were maintained lower @ 1 $\log_{10}$ CFU in phage treated groups which are given a cocktail of 3 phages to broiler chickens by gavage and feed when compared to untreated control. Chinivasagam et al. (2020) gave a variety of Campylobacter phages orally to 47-day-old broiler chickens, and 28 hours after treatment, they reported a considerable bacterial decrease of 1–3 $\log_{10}$ CFUs/g in the ceca. Reducing *C. jejuni* levels in hens using bacteriophage control could minimize the risk of infection and illness to humans caused by consuming infected chicken products (Richards et al., 2019). The group III phage vB CjM-LmqsCP1-1 and the group II phage vB CcM-LmqsCP218-2c2 were shown to be viable for application against *C. coli* and *C. jejuni* (Steffan et al., 2022).

Clostridiosis The causative agent of necrotic enteritis is *Clostridium perfringes*. The pathogenicity of this bacterium is due to its toxins and hydrolases. Miller et al. (2010) used 42-days old 900 birds which were experimentally infected with *Clostridium perfringens* and then administered 5 phage cocktails at 10^5 PFU/mL by oral gavage or drinking water. This resulted in a reduction of mortality by 92% compared to the untreated group. The specific cocktail (INT-401) which is used in the experiment resulted in an increase in weight gain and feed conversion ratio in both

Table 1. Doses of phages for regular use in poutry industry

Reference	Organism to be challenged	Phage Inoculum	Age of the bird	Delivery Method of Phages	Schedule of Phage Delivery	Sampling Times	Significant ($P < 0.05$) Effect Observed	Bacterial Enume-ration Method	Number of Inputs; Total Observations
Adhikari et al. (2017)	*Salmonella enterica* Enteritidis	Two phage types, preparation methods not specified (NS)	>14 days	diet	Phages delivered multiple times both before and after challenge	3, 7 days after-post phage treatment	Yes	Viable cell count	2; 48
Atterbury et al. (2007)	*Salmonella enterica* Enteritidis	Single phage type suspended in PBS with 30% wt/vol CaCO*f*	>14 days	Oral	Phages delivered once after bacterial challenge	3 days post-phage treatment	Yes(10^{11} pfu/bird)	Viable cell count	3; 25
Bardina et al. (2012)	*Salmonella enterica* Typhimurium	Three phage types suspended in Luria Bertani medium	<14 days	Oral	Phages are treated multiple times before and after challenge	6, 10, 17 days post-initial phage treatment	Yes, when treated < 4 days after challenge	Viable cell count	3; 32
Borie et al. (2009)	*Salmonella enterica* Enteritidis	Three phage types, preparation method NS	<14 days	Aerosol spray	Phages delivered twice before bacterial challenge	8 days post-initial phage treatment	No	Most probable number	1; 30
Borie et al. (2008)	*Salmonella enterica* Enteritidis	Three phage types, preparation method NS	<14 days	Aerosol spray	Phages delivered once before bacterial challenge	11 days post-phage treatment	Yes	Most probable number	3; 66
Colom et al. (2015)	*Salmonella enterica* Typhimurium	Three phage types in Mg SO,, buffer or encapsulated	<14 days	Oral	Phages delivered multiple times before and after challenge	4, 11, 16 days post-initial phage treatment	Yes	Most probable number	6; 126
El-Shibiny et al. (2009)	*Campylobacter jejuni* and *C. coli*	Single phage type*f* in 30% wt/vol CaCO	>14 days	Oral	Phages treated once after bacterial challenge	3 days post-phage treatment	Yes, more effective at 10y pfu/bird; more for *C. jejuni*	Viable cell count	2; 24
Fischer et al. (2013)	*Campylobacter jejuni*	Four different phage types or one in SM buffer with 30% wt/vol CaCO*f*	<14 days	Oral	Phages treated once after bacterial challenge	3, 14, 28 days post-phage treatment	Yes	Viable cell count	6; 99
Lim et al. (2012)	*Salmonella enterica* Enteritidis	Single phage type, preparation method NS	<14 days	Diet	Phages treated many times after challenge	7, 14, 21 days post-initial phage treatment	Yes	Viable cell count	3; 120
Loc Carrillo et al. (2005)	*Campylobacter jejuni*	Single phage type in 30% wt/vol CaCO*f*	>14 days	Oral	Phages treated once after bacterial challenge	3 days post-phage treatment	Yes	Viable cell count	3; 26

phages in the water group and phage in the feed group when compared to the untreated group.

Improving poultry production and nutrient intake

Numerous investigations have focused on the creation of natural chemicals as replacements for antibiotics. These can be included into feed to decrease the bacteria in the gut andto improve the body's defense, health, growth, and productivity of chicken flocks (Islam et al., 2020). There aren't many research on the usage or supplementation of phages to enhance poultry growth performance and dietary absorption. There are different doses Of phages for regular use in poutry industry, few of them are mentioned in (Table1). Commercial goods containing phages against various bacteria at levels of 0.05 and 0.1% did not affect the nutrient intake, FCR, or apparent overall intestinal digestibility of broiler chickens, according to (Upadhaya et al., 2021). At days 1–7 and 22–35, however, body weight (BW) growth was proportionally increased by increasing titers of phages. According to Upadhaya et al. (2021), the phage supplementation enhanced the growth of Lactobacillus and other beneficial bacteria in the broiler's intestines through competitive exclusion. Feed added with phages at 0.1 and 0.2% showed greater BW increase and lower FCR than those supplied with 0.05%, according to a similar research by Kim et al. (2013). A study by Sarrami et al. (2022) found that oral BP (at a level of 1–1.5 g/kg diet) could eradicate harmful bacteria, alter the GIT's microbial composition, and provide additional advantages to the host, including raising the concentration of SCFAs, strengthening the immune system, and enhancing intestinal morphology. Some of the positive effects of bacteriophages may be influenced by the up-regulation of the IL-10 gene, which alters the GIT's immune response and activates the subsequent signaling pathways, which improves the metabolism of cells of the epithelium by up-regulating the PPARγ gene and suppressing the PGC-1α gene, respectively (Sarrami et al., 2022).

Conclusion

Antibiotic resistant pathogens responsible for zoonotic diseases are a major global public health concern in recent decades. We have to move forward with a global goal of reduction of antibiotic use in animal husbandry. A large amount of research has been done in intensive farming systems which revealed that the pathogenic organisms can be reduced significantly using bacteriophages resulting. The bacteriophages improving the gut health by increasing the non pathogenic (beneficial) bacteria at the intestine level thereby improving the nutrient absorption resulting improving the production performance of the bird by maintaining the health. Resulting in a beneficial effect on human and animal health globally. The emergence of phage resistance bacterial pathogens and multidrug resistance both are analogous to each other. To maintain the efficacy and control of bacteriophages resistance, regular reformulation of phage cocktails and regular cycling of cocktails with different concentrations are to be done. Keeping the global challenges in mind, to meet the growing meat demand globally, viable alternative strategies to antibiotics will be required to control the adverse effects like multidrug resistance, antibiotic failure so that treatments like antibiotic chemotherapy and vaccination will offer a panacea.

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