IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 2 Ser. IV (Mar –Apr 2020), PP 23-36
www.Iosrjournals.Org

Bacteriophages as Bio-control agent against Food-Borne Pathogen *E. coli* O157:H7

Ngene, Anayochukwu Chibuike[1,2*],Aguiyi, John C.[1], Uzal, Umar[1], Egbere, John O.[3], Onyimba, Isaac Amechi[4], Umera, Arinze Emmanuel[1], Nnadi, Nnaemeka Emmanuel[5].

1. Africa Center of Excellence in Phytomedicine Research and Development, University of Jos, Plateau State, Nigeria
2. Department of Microbiology, College of Natural Sciences, Michael Okpara University of Agriculture Umudike, Abia State, Nigeria
3. Department of Microbiology, Faculty of Natural Sciences, University of Jos, Plateau State, Nigeria
4. Department of Science Laboratory Technology, Faculty of Natural Sciences, University of Jos, Plateau State, Nigeria
5. Department of Microbiology, Faculty of Natural Sciences, Plateau State University Bokkos, Plateau State, Nigeria

Abstract: *Escherichia coli O157:H7 is a foodborne pathogen that causes disease in humans.It was first recognized as a human pathogen following an outbreak of hemorrhagic colitis associated with the consumption of undercooked ground beef in 1982. There have been several reports ofE. coli O157:H7-related outbreaks throughout the world especially developing countries such as Nigeria.Food-borne pathogenassociated with E.coli O157:H7 outbreaks is still being reported as the cause of hospitalizations and deathsdespite advances in food sanitation techniques and pathogen surveillance in developed countries. A promising approach that addresses most of these challenges is bacteriophage biocontrol, a natural and green method that uses lytic bacteriophages isolated from the environment to selectively target and eliminate pathogenic bacteriaor reduce their levels in foods. Starting from the initial conception of using bacteriophages on foods, a good number of research reports have described the use of bacteriophage biocontrol to selectively target a variety of bacterial pathogens in different foods, which ranges from fresh vegetables and fruits to ready-to-eat cooked meats. As some challenges persists, bacteriophage biocontrol is increasingly recognized as an attractive modal value in food safety and a natural way of eliminating pathogenic bacteria from foods. This review summarizes recent development and perspectives of phages used as biocontrol agents against foodborne pathogen E. coli O157:H7 and their adjoining phage therapies are discussed.*

Keywords: *Bacteriophages, phages, E. coli O157:H7, biocontrol, foodborne pathogen, antibacterial*

Date of Submission: 13-04-2020 Date of Acceptance: 28-04-2020

I. Introduction

Based on the Latin proverb, we all are born between the urine and faeces.Thus, we acquire from birth the faecal flora of our mothers. Over a century ago, Escherich explained the bacteria he isolated from a human neonates faeces as *Bacterium colicommune*. He revealed that the organisms now called as *Escherichia coli* were present in the intestinal contents of humans and faeces and were considered as commensal organisms [1,2].*E. coli* O157:H7 was first identified as a possible human pathogen in 1975 in a California patient with bloody diarrhea and was first associated with a foodborne (ground beef) outbreak of disease in 1982 [3]. This serotype (defined by its O and H surface antigens) and some non-O157 serotypes of *E. coli* produce verocytotoxins, also called Shiga-like toxins because of their similarity to toxins produced by *Shigella dysenteriae*. These *E. coli* are called VTEC (verocytotoxin-producing *E. coli*), STEC (Shiga-toxin producing *E. coli*), and also EHEC (enterohemorrhagic *E. coli*) because of the symptoms they produce [4, 5].

Enterohemorrhagic *Escherichia coli* (EHEC) has predominantly emerged in recent years as the causative agent of hemorrhagic colitis in humans. This illness, with characteristic symptoms of bloody diarrhea and abdominal cramps, can progress into a more severe, life-threatening complication known as hemolytic uremic syndrome (HUS). The pathogenicity of EHEC appears to be associated with a number of virulence factors, including the production of several cytotoxins [6, 7]. *Escherichia coli* strains that cause diarrhoea includes; enteropathogenic (EPEC), enterohaemorrhagic (EHEC) and enterotoxigenic (ETEC), enteroinvasive (EIEC) strains. Recently, enteroaggregative *E. coli* (EAggEC) has been established to be a diarrhoegenic strain.

Among EHEC strains, *E. coli* O157:H7 is one of the most studied foodborne pathogens, because of its peculiar tolerance to some physical and chemical treatments, low dose infectiveness, widespread diffusion and severity of illness [8].Outbreaks are most commonly linked with the consumption of undercooked meat. The most common pathway among *E. coli* O157:H7 outbreaks is associated with the consumption of ground beef. *E. coli* O157:H7 has also been found in pigs, chickens, turkeys, wild animals, seafood, and leafy vegetables [9].

Bacteriophages are viruses capable of lysing bacteria, and specific lytic phages can kill pathogenic bacteria in their own habitat. Phages are ubiquitous in nature and can often be found in a variety of environments related to their host such as soil, sewage, water, manure, animal and produce farms, as well as different food processing plant effluents. The application of bacteriophages as a food safety intervention has been recently investigated and a few commercial preparations have been approved and marketed. Bacteriophages are often used in high concentrations to inactivate foodborne pathogens, such as *Escherichia coli* O157:H7, *Salmonella*, *Listeria*, and *Campylobacter* in different foods [10, 11, 12, 13]. Also, in production facilities, phages also have been used to control specific bacteria at pre-harvest and post-harvest stages of food production and storage. In Russia, several phage formulations are now being sold as registered medicine [14]. The Food and Drug Administration (FDA) has approved Listeria specific phages for use in foods [15] indicating the promising use of bacteriophages in food applications.Given this renewed interest on phage biocontrol of pathogens in food products, several phagebased products that have shown considerable potential have been approved for use and are already commercially available in the market in countries like North-America and Europe. LISTEXTM P100 and ListshieldTM (LMP-103 TM) which have been approved by the US Department of Agriculture (USDA) for the control of *Listeria monocytogenes* and EcoShieldTM has also been permitted for the control of*E. coli* O157:H7. Similarly, SalmoFresh another phage-based preparation received Generally Recognized as Safe (GRAS) recognition from the FDA in 2013 for direct applications onto meat products and fresh produce. In the West, all these products have been received and applied by the food producers as natural antimicrobials employed in reducing the risk of food-borne human diseases due to the consumption of contaminated foods [16].In this context, bacteriophages have potential as an alternative to antibiotics or other conventional chemical control methods against bacterial pathogens. Felix d'Hérelle, the discoverer of bacteriophages, first introduced the idea of phage therapy in the beginning of the 20th century [17].This review is focused on applications of wild type bacteriophages for improving the safety of foods against foodborne pathogen *E. coli* O157:H7.

II. *E. coli* O157:H7

Escherichia coli is a bacterium that normally lives in the intestines of humans and animals. Although most types of these bacteria are harmless, several produce toxins that cause illness. Some strains of *E. coli*, including *E. coli* O157:H7, produce toxins known as Shiga toxins and are called "Shiga toxin-producing" *E. coli* (STEC). These may cause severe diarrhea and kidney damage [18].In the United States the first confirmed case of *E.coli* O157:H7 was in 1975 from a California woman with bloody diarrhoea. Less than 3 week old calf with colibacillosis in Argentina in 1977 was the first reported isolation of *E.coli* O157:H7 from cattle. The bacterium was first identified as a human pathogen in 1982, when it was associated with two food borne outbreaks of Hemorrhagic colitis. Since then O157 VTEC have been identified in many outbreaks and in sporadic cases of bloody diarrhoea in North America and Great Britain and a close association has been established between VTEC and haemorrhagic uremic syndrome (HUS) [19].

2.1 Characteristics of *E.coli* O157:H7

Several uncommoncharacteristics possess bymost strains of *E.coli* O157:H7to other *E.coli*.

1. **Acid tolerance**: Unlike most food borne pathogens, *E.coli* O157:H7 uniquely tolerant to acidic environments. Acid tolerance is a complex phenomenon, both growth phase dependent and inducible. *E.coli* cells in stationary phase of growth are substantially more acid tolerant than cells in the exponential phase. Genes regulated by the rpoS sigma factor operon is associated with increased tolerance [20, 21, 22] examined three mechanisms of acid resistance, that is,oxidative-arginine dependent and glutamate dependent, and found that the microorganisms overall acid tolerance is contributed by all the three. Survival in acidic foods is enhanced by the induction of acid tolerance in *E.coli* [20].
2. **Antibiotic resistance**: Sufficient evidence indicates that the bacterium is resistant to most antibiotics [23, 24].
3. **Thermal inactivation**: Studies on the thermal sensitivity of *E.coli* O157:H7 in ground beef have revealed that the pathogen has no unusual resistance to heat, with D values at 57.2°C,60°C, 62.8°C and 64.3°C of 270,45,24 and 9.6 s respectively. It has also been determined that Pasteurization of milk(72°C,16.2 s) to be an effective treatment that will kill more than 10^4*E.coli* O157:H7 cells per ml.Proper heating of foods of animal origin (63°C) is an important critical controlpoint to ensure inactivation of *E. coli* O157:H7 [25].

4. **Inability to grow well**: It is important to note that many VTEC strains do not grow well at 44°C, if at all, above 44°C.The minimum growth temperature for *E. coli* O157:H7 under otherwise optimal condition is approximately 8 to 10°C [26].
5. **Inability to ferment sorbitol within 24 hours**: Most but not all O157 VTEC strains do not ferment sorbitol.
6. **Inability to produce ß-glucoronidase**: Most of the O157 VTEC strains will not hydrolyze 4-methyl umbelliferyl-D-glucoronide [27].
7. **Inability to produce gas and indole at 44°C**: Hence such methods would probably fail to detect VTEC [28].
8. **Possession of an attaching and effacing (*eae*) gene**: This property contributes to VTEC to establish its pathogenicity [8].
9. **Carriage of a 60-MDa plasmid**: A plasmid (pO157) of approximately 60 MD that contains DNA sequences common to plasmids present in other serotypes of VTEC isolated from patients with Haemorrhagic colitisassociated with human illness harbor *E. coli* O157:H7 isolates. It was hypothesized that the plasmid is believed to play a role in the pathogenicity of disease, but its function is unclear [27, 28].
10. Expression of an uncommon 5,000 to 8,000 molecular weight outer membrane protein.[29].

2.2 Reservoirs of *E. coli* O157:H7

Several reservoirs and sources of *E. coli* O157:H7 have been identified. The role of cattle as a reservoir of the pathogens association with*E. coli* O157:H7 led to the investigation of undercooked ground beef and raw rice. Several surveys of faecal shedding of *E. coli* O157:H7 led to the following general observations; Adult animals tend to carry less*E. coli* O157:H7 than young ones [30].Among positive herds, prevalence of faecal excretion varies substantially [30].The levels of *E.coli* O157:H7 in calf faeces range from less than 10^{2} CFU/g to 10^{5} CFU/g [30]. *E.coli* O157:H7 frequent faecal shedding is intermittent and of short duration, i.e. several weeks to months [5, 31]. From faeces of the same animal or different animals within the same herd, more than one strain of *E. coli* O157:H7 can be isolated. *E. coli* O157:H7 have been experimentally infected with Calves[31].

2.3 Novel Vehicles of Transmission

Most outbreakshas accounted for consumption of contaminated undercookedground-beef products; however, raw milk was also implicated in several outbreaks in the United States and Canada. Another well-documented route of infection is improper hygiene with secondary spread from person-to-person contact [6, 7]. Several foodborne outbreaks of serotype O157:H7 in the last few years however, have implicated unique and seemingly unlikely vehicles of infection: among them are acidic foods, fruits, salad vegetables, yogurt, and water [32].

1. **Water:** Several recent incidents show that both drinking water and recreational water can serve as vehicles for transmitting serotype O157:H7 infections. The first and largest waterborne outbreak associated with this pathogen occurred in Missouri in 1989 [33]. Of the more than 240 people infected, 32 were hospitalized, and four died. The source of the outbreak was not identified, but backflow during a water main break might have contaminated the drinking water supply [33]. Like most *E. coli*,effects of chlorine affects serotype O157:H7 isolates. Hence, adjustments in the chlorination of the drinking water supply during repairs to the water main might have prevented the outbreak [33]. An outbreak caused by serotype O157:H7 and *S. sonnei* in 1991 may have involved recreational lake water in the vicinity of Portland, Oregon. Of the 59 people affected, 21 (all children) were infected by serotype O157:H7 [34]. An epidemiologic survey showed that those who became ill had swum in the lake during the previous 3-week period. When the swimmers swallowed lake water that was faecally contaminated by other bathers, transmission probably occurred. The lengthy period during which people became infected suggests that these pathogens can remain viable in water for a long time, or that the water was repeatedly re-contaminated. Fecal contamination of recreational water by bathers, especially small children, is not uncommon; however, the contaminants are usually diluted quickly by the large volume of water in recreational lakes, bays, or rivers. That swallowing a small amount of lake water can cause illness suggests that the pathogen has a low infectious dose [34]. This fact is already well established for *Shigella* and seems to be consistent with recent epidemiologic data from foodborne outbreaks associated with serotype O157:H7. A similar incident, implicating water from a children's paddling pool, was reported in Scotland in 1992 [35]. The available data suggested that a child with diarrhea had played in the pool faecally contaminated the water with serotype O157, although epidemiologic evidence was not conclusive. Because the pool water was not changed or disinfected, it became the vehicle of infection for two other neighborhood children, who in turn infected others by person-to-person contact [32].
2. **Acidic foods**: In the Retail Food Store Sanitation Code of the U.S. Food and Drug Administration, foods with a pH value of less than 4.6 are generally regarded as low risk in terms of food safety. However, several recent disease outbreaks attributable to serotype O157:H7 have shown that this pathogen can persist in

foods with low pH. In the fall of 1991, an outbreak of serotype O157:H7 that affected 23 persons was traced to the consumption of fresh-pressed apple cider [36]. The implicated cider, made from unwashed "dropped" apples at a farm, had a pH value of 3.7 to 3.9, was not pasteurized, and contained no preservatives. Although previous outbreak of *Salmonella enterica serova Typhimurium*had been implicated in apple cider,because of its high acidity, it is not a common vehicle of enteric infection. Several laboratory studies have subsequently demonstrated that isolates of serotype O157:H7 can tolerate acidic conditions. Some strains persist in media with pH values as low as 2.0 (8), and in cold (8°C) apple cider for 10 to 31 days [36, 37]. Although the source of serotype O157:H7 in the cider that caused illness was never fully established, it was suspected that the dropped apples had been contaminated by cow manure. The acidity tolerance of O157:H7 serotypeprovided evidencein 1993, when another acidic food was implicated in a series of restaurant outbreaks that infected at least 48 persons. Although the source of the outbreaks was not conclusively identified, epidemiologic investigations and other data implicated mayonnaise or mayonnaise-based dressing and sauces. Samples of mayonnaise had a pH of 3.6 to 3.9, and the sauces prepared from it were also acidic, with pH levels of 3.6 to 4.4 [38]. After this outbreak, several studies confirmed that although isolates of serotype O157:H7 do not multiply under these conditions, they can persist in commercial mayonnaise up to 55 days at 5°C [38, 39]. How the mayonnaise became contaminated with serotype O157:H7 was not determined; however, improper handling of bulk mayonnaise or cross-contamination with meat juices or meat products was suspected.

3. **Other vehicles of transmission**: Recently, several other unique vehicles have been implicated in foodborne outbreaks associated with serotype O157:H7. A 1993 outbreak in an Oregon restaurant was apparently caused by the consumption of cantaloupe or other items from the salad bar, which were most likely cross-contaminated by meat products during preparation. One study showed thatserotype O157:H7 can survive and grow on salad vegetables stored at 12°C and 21°C for up to 14 days [40]. An outbreak in the United Kingdom in 1991 was traced to the consumption of yogurt, which infected 16 persons, 11 of them children [41]. Although past outbreak has been caused by consumption of raw milk, serotype O157:H7does not usually survive the pasteurization process and thus is susceptible to heat treatment. Even though the implicated yogurt was prepared from pasteurized milk, the milk might have become contaminated with serotype O157:H7 after pasteurization. A complicated incident was reported from northern Italy, where 15 cases ofHemolytic uremic syndrome(HUS), caused by serotype O157 and other EHEC serotypes, was recorded over a five-month period in 1993 [42]. However, data from the epidemiologic investigations suggested that contact with live poultry or with chicken coops may have been the source of infection, even though no toxin-producing EHEC strains were isolated from poultry feces. A recent study showed that inoculating 1-day-old chicks with strains of serotype O157:H7 resulted in rapid colonization of the caecal tissue of the chicks. The chicks then became long-term (up to 11 months) shedders of serotype O157:H7, and this microorganism was subsequently recovered from the shells of their eggs [43]. It is conceivable, therefore, that live poultry were the source of infection in the outbreaks reported from northern Italy. In December 1994, dry cured salami was implicated as the source of serotype O157:H7 in a disease outbreak in the state of Washington [32]. A prior study showed that although isolates of serotype O157:H7 do not grow in seeded sausage batter, they can tolerate the acidity produced during sausage fermentation and survive the drying and the cold storage associated with the preparation of dry sausages [44]. Fermented sausages can attain a pH as low as 4.8 [44]. The ability of serotype O157:H7 isolates to persist under these conditions is consistent with the acid-tolerant properties this organism exhibited in the previously discussed studies with apple cider [36] and mayonnaise [38]. Although the consumption of bovine products still accounts for most of the serotype O157:H7 infections, the incidents described above show that other food types can also serve as vehicles in transmitting infections with this serotype [32].

2.*4 E. coli* O157:H7 threat to humanity

Over the last years, despite the strict controls to prevent food borne diseases; enterohaemorrhagic *Escherichia coli* (*E. coli*) *E. coli* (EHEC) serogroup O157 has emerged as a worldwide threat to public health following its first identification in an outbreak occurred by year 1982 [45]. Centers for Disease Control and Prevention, 2014 approximates that *E. coli* O157:H7 causes just about 73,400 illnesses and 60 deaths annually in the United States pointed out that antibiotic resistant *E. coli* pose a growing threat. Cases of foodborne infections and even deaths associated with the consumption of food contaminated with *E. coli* O157:H7 occur regularly in many countries throughout the world [46]. In contrast to developed nations, African countries are faced with the problem of poor health systems and inefficient surveillance or pathogen tracking systems exacerbating the burden of disease in these nations. In addition, the frequent occurrence of *E. coli* O157:H7 infections is a serious additional problem to disease-burden of these nations and thus requires effective control measures [16].

III. Bacteriophages

Frederick Twort and Felix d'Hérelle are accredited as the founding fathers of biology of phages having discovered that bacteriophages (bacteria eaters) are present in every environment wherever bacteria are found [47, 48]. During World War I, the unsanitary conditions in the trenches on the battle-fronts caused infections such as dysentery affecting numerous soldiers. The bacterial cause of these infections was studied by Felix d'Hérelle and identified *Shigella* as the etiologic agent of this rampaging infectious disease. The existence of a propagatable bactericidal agent in 1915 was demonstrated by Frederick Twort while independently (or not) Felix d'Hérelle co-incubated fecal filtrates with the isolated bacteria in petri dishes resulting in the elimination of the bacteria (d'Hérelle's prior knowledge of Twort's research remainsuncertain,reviewedhere [49]. Theco-existenceandrelationship between bacteriaandtheirinfectingphageswasahistoriconethat was first described createdtheopportunitytodeveloptreatments against bacterial infections for which therapies were not available at that time. During the 1920's and 1930's d'Hérelle blazed the trail of phage therapy by successfully developing phage-based treatments against a range of human infections including those caused by *Shigella dysenteriae*, *Salmonella typhi*, *Escherichia coli*, *Pasteurella multocida*, and *Vibrio cholera*[50].

3.1 Life Cycle of Bacteriophages

All known phages can be divided in two groups according to the type of infection. One is characterized by a lytic infection and the other by a lysogenic (temperate) type of infection (Figure 1). In the first form of infection, DNA release induces switching of the protein machinery of the host bacterium for the benefit of infectious agents to produce 50-200 new phages. To make more new phages requires nearly all the resources of the cell, which becomes weak and bursts. In other words, death of the host bacterial cell is caused by lysis, resulting to new phages release into the extracellular space. In other hand, lysogenic infection is characterized by integration of the phage DNA into the genome of host cell, though it may also exist as a plasmid. Phage DNA incorporated will be replicated along with the genome of bacteria host and viral DNA will be inherited by the new bacteria. Without major metabolic consequences, such transition of viral DNA could take placethrough several generations of bacterium. Eventually the phage genes impeding the bacterium stateat certain conditionswill revert to the lytic cycle, leading to release of fully assembled phages (Figure 1). Analysis of phages with lysogenic or lytic mode of infection has shown that there is a tremendous variety of bacteriophages with variations in properties for each type of infection. Moreover, under certain conditions, some species were able to change the mode of infection, especially if the number of host cells was falling down. Temperate phages are not suitable for the phage therapy [51, 52].

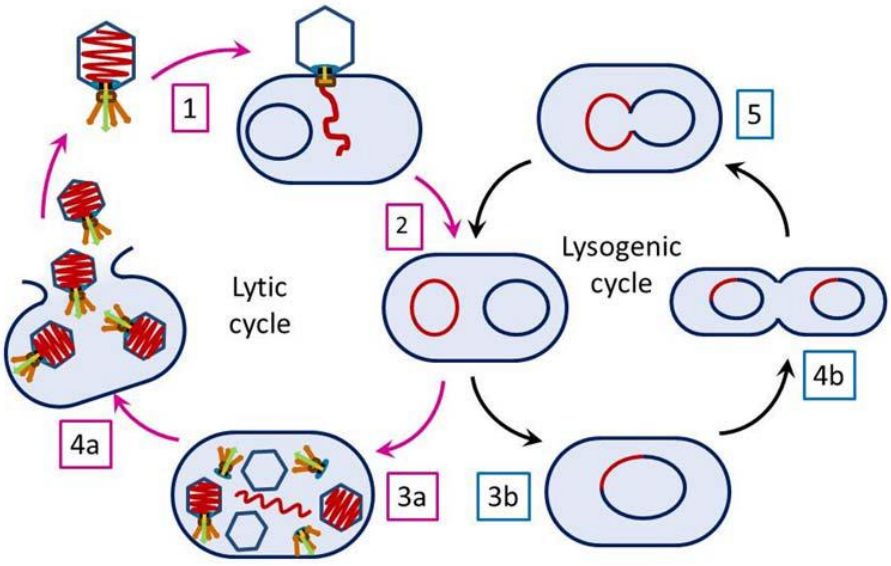

Figure 1. Two cycles of bacteriophage reproduction. 1 - Phage attaches the host cell and injects DNA; 2 – Phage DNA enters lytic or lysogenic cycle; 3a – New phage DNA and proteins are synthesized and virions are assembled; 4a –releasing virions through cell lysis; 3b and 4b – steps of lysogenic cycle: integration of the phage genome within the bacterial chromosome (becomes prophage) with normal reproduction of bacteria; 5 - Under some conditions, the prophage excises from the bacterial chromosome and initiates the lytic cycle. *(PDF) Bacteriophages and Their Structural Organization*. Available from: https://www.researchgate.net/publication/221928631_Bacteriophages_and_Their_Structural_Organisation [accessed Feb 29 2020]; [51].

IV. Phages As Biocontrol Agents

4.1 Phages in Agriculture: Phagesareinherentlyhighlyspecific towardsbacterial hosts. This characteristic asbothpositive and negative aspectsthatisbeneficial intermsofavoidingnegativeeffectsonmicrobiota of the host andahindrancewhenitcomesto detection and killing of the target pathogen [53, 54].The goal of sustainable agriculture is to implement practices that will meet healthy disease-free animals and plants,minimize the impact of agricultural practices on the environment and provide safe food for a growing global population. As antimicrobial agents, the development of phages in plant and animal production systems follows a like path in the initial discovery stage however the implementation processes becomes divergent. In the following sections we discuss the progress made in the use of phages in plant and animal farming, focusing on the challenges and success stories reported in scientific literature [55, 56].

4.2 Phages in Food Animal Production: The vast majority of antibiotics by volume consumed worldwide are for veterinary purposes, predominantlyinlarge-scale and intensive animalproductionsystems,suchaslivestock, poultry, dairy, and aquaculture [57, 58]. Animal husbandry practices widely use antibiotics therapeutically to treat infectious diseases, as well as non-therapeutically to prevent the spread of disease (prophylaxis) and to promote growth. However, controversy surrounds the widespread use of antibiotics for animal production, as their possible misuse and overuse is driving antibiotic microbial resistance. The extended practice of exposure for example, to sub-therapeutic antibiotic doses, the context in which growth-promoting and prophylactic antibiotics are delivered employ an inestimable amount of selective pressure toward the emergence of antimicrobial resistance (AMR) [59, 60]. Furthermore,AMR genes andantimicrobial resistance bacteria of animal origin can then be transmitted to humans throughfood distribution, environmental contamination, or direct contact with farm animals [61, 62]. To keep animals healthy and maintain productivity,intensive animal production systems necessitate antibiotics, and with rising incomes in transitioning countries expected to boost antibiotic consumption by 67% by 2030 [63], this presents a major health risk to humans and animals. The World Health Organization, the European Commission, the Centers for Disease Control and Prevention, and Health Canada, to name a few, all support immediate antimicrobial stewardship in animal food production, targeted primarily at eliminating or reducing the nontherapeutic use of medically important antibiotics. Outright elimination of prophylactic antimicrobials may not be feasible inintensiveanimalproductionsystemsduetoworldwideincreasingdemandforprotein,thepotential compromise in animal health and welfare, and in human health and food safety. In place of antibiotics, phage is a promising option in animal and food production to maintain animal health and limit the transfer of AMR and zoonotic pathogens that may be harmful to consumers [64].

4.3 Bacteriophages that fight ZoonoticPathogens: As a pre-harvest intervention, phages offer a non-antibiotic method to improve food safety to reduce zoonotic pathogens from the food supply. For instance, contaminated pork, beef, poultry, and fish have led to food-related disease food poisoning. Meat products often contamination by foodborne pathogen occurs during processing when infected animal faeces are expose to carcasses. *Campylobacter jejuni* the causative agent of Campylobacteriosis is the most frequent food-borne human enteritis in developed countries,poultry meat being the major source. [65] showed that an antacid solution containing phages administered orally could effectively decolonize the gut of birds experimentally colonized with *C. jejuni*. Under commercial conditions, phage decontamination variably was highly successful. When a phage cocktail was added to the drinking water at three commercial farms with broilers confirmed to be colonized with *Campylobacter* spp., only one farm experienced a reduction in bacterial load (<50 CFU/g) in faecal samples [66]. For the other two farms, no significant reduction occurred for undetermined reasons. Salmonellosis is another common cause of gastroenteritis in humans. Pigs can become colonized with *Salmonella* spp. from contaminated trailers and holding pens, resulting in increased pathogen shedding just prior to processing. [58] showed that administration of a phage cocktail at the time of experimental inoculation with *Salmonella entericaserovar Typhimurium* reduced bacterial load in the infected piglets. Caecal and ileal *Salmonella* concentrations was reduced by phage cocktail significantly by up to 95% after being in a highly contaminated holding pen. *S. enteritidis* is also a prevalent foodborne pathogen, its main reservoir being the eggshell. A significant decrease in bacterial prevalence of incidence of up to 80% by use of a mixture of three different *Salmonella*-specific phages to reduce *S. enteritidis* colonization in the ceca of laying hens resulted[67]. *E. coli* is typically a commensal member of human and animal microbiota. However, certain strains can cause a variety of human diseases, including urinary tract infections, haemorrhagic colitis, appendicitis and septicaemia. Those referred to as Vero-Toxigenic *E. coli* (VTEC) are the most notorious zoonotic strains. The strain 0157:H7 is the most common member of the group which resides in the cattle gut. The population of 0157:H7 in the gut was reduced by a cocktail of phages isolated from the faeces [68]. Upon necropsy,while ruminal load was not significantly changed, likely due to a relatively low starting population,*E. coli* populations were found to be reduced in both the cecum and colon[68].

Table 1
Experimental studies using bacteriophages as biocontrol agents against bacterial pathogens.

Target Species	Disease/Issue	Animal/Plant	Study
Escherichia coli	respiratory infection	poultry	[69, 70]
Escherichia coli	colitis	sheep	[68]
Clostridium perfringens	necrotic enteritis	poultry	[71]
Staphylococcus aureus	Mastitis	Bovine	[72, 73]
Vibrio anguillarum	Vibriosis	Fish	[74, 75]
Vibrio harveyi	Vibriosis	Shrimp	[76]
Pseudomonas plecoglossicida	haemorrhagic ascites	Fish	[77, 78]
Campylobacter jejuni	Zoonotic	Poultry	[79, 66]
Salmonella enterica serovar Typhimurium	Zoonotic	Swine	[58]
Salmonella enteriditis	Zoonotic	Poultry	[67]
Xanthomonas campestris pv. Campestris	cabbage rot	Cabbage	[80]
Pectobacterium atrosepticum	soft rot	Potato	[81, 82]
Pantoea stewartii	Stewart's wilt	Corn	[83]
Dickeya solani, Pectobacterium spp.	soft rot/blackleg	potato	[82, 84]
Ralstonia solanacearum	bacterial wilt	tomato	[85]
Erwinia amylovora	fire blight	apple/pear	[81, 86, 87]
Xylella fastidiosa	Pierce's disease	grape	[88]
Xanthomonas axonopodis pv. Citri	canker	citrus	[89]
Xanthomonas axonopodis pv. citrumelo	bacterial spot	citrus	[90]
Pseudomonas syringae pv. porri	bacterial blight	leak	[91]
Pseudomonas syringae pv. actinidae	canker	kiwifruit	[92]

V. "Bacteriophages" a solution to biocontrol of foodborne pathogen *E. coli* O157:H7

Escherichia coli are rod-shaped, Gram-negative, naturally found in the human intestine andarebeneficialforourhealthandwellbeing;forexample,they help indigestionoffood and maintenance of a robust immune system. However, some *E. coli* strains can cause diseases inhumans. Forexample,theShigatoxinproducing*E. coli*serotype O157:H7 found at times incontaminated foods (especially beef) or water can enter thehumangastrointestinaltractandtrigger disease, with symptoms including hemorrhagic diarrhea and abdominal cramping. In immunocompetent individuals these infections are self-limiting but can potentially be life-threatening in very young or old patients. Globally, it has been estimated that more than one million cases of foodborne illness and over one hundred deaths could be attributed to Shiga toxin-producing *E. coli*, including the O157:H7 serotype [93]. *E. coli*-specificphagepreparations in recentworkhasdemonstrated to be effectivewhenusedto treatfreshvegetables [94] andbothUltra-High-Temperature(UHT)treatedandrawmilk contaminated with *E. coli*[95].

In the first study, on green pepper slices and spinach leaves, *E. coli* O157:H7 level were reduced by a single phage by approximately 1^{-4} logs, and the initial reduction was maintained at 4^0C while some regrowth was seen at 25^0C. In the second study, the levels of *E. coli* were reduced to a level that they were undetectable in bothraw milk and UHT when a cocktail of two or three phages was used. It was observed that all samples treated with the three-phage preparation, this reduction was maintained over storage at both 4 and 25^0C; in contrast, there was regrowth of the *E. coli* strain in the samples treated with the two-phage cocktail. While the underlying reasons are not well understood, it is possible that the three-phage cocktail provided better management of resistance versus a two-phage cocktail, andtheenhancedefficacyofmulti-phagecocktailshasbeendemonstratedforotherphage preparations previously [96]. Even though the underlying reasons for this phenomenon have not been carefully determined, it is possible that having multiple phages in a phage cocktail reduces the risk of the emergence of phage-resistant mutants, because multiple mutations would be required to render a given bacterial cell resistant to not one, but multiple phages in the cocktail, assuming the phages target distinct cellular structures. This idea is essentially the same as the multi-hurdle approach, which on using a combination of antibacterial strategies proposes to discourage the development of bacterial resistance [97].

One of the promising "new" treatments that is more and more highlighted among other things during the recent UN General Assembly is phage therapy. The therapeutic use of bacteriophages (phages), the viruses of bacteria to treat bacterial infections [98]. Phages control their host's bacteria, on our planet. They were immediately applied in medicine when discovered in the early twentieth century. It soon appeared that phages are exquisitely host-specific. Majority of phages can only lyse a subset of a bacterial species. Before medical practitioners can treat a patient, they must thus first know which bacteria cause the infections. As could be expected, it was shown that bacteria could also evolve to evade phage infection, even when potent phages are applied simultaneously [99]. The main advantage of phages over antibiotics however, is their ability to mutate at least as fast as their host bacteria. This enables them to evolve new infectivity and thus regain the "upper hand"

over bacteria. Phages and bacteria are thus involved in a continuous arms race of co-evolving infectivity and defense mechanisms. The advent of broad-spectrum antibiotics, empirically could be used to target a wide range of bacterial infections,heraldedthedeclineofphagetherapyintheWesternworld. The triumph of the many phage applications in the past, mainly on the east side of the Iron Curtain, where phage therapy remained a recognized treatment, together with the rise in the number of virtually untreatable bacterial infections, has created a growing demand for phage therapy. Some successful intravenous applications of phages to treat terminally ill patients in the Western world have recently been published in the scientific literature [100, 101, 102].

Table 2
Summaryofstudiesofdirectphageapplicationontoavarietyoffoods

Bacterium	Phages	Observations
***Escherichia coli* O157:H7**	e11/2,pp01,e4/1c	After incubation at 37◦C, a three-phage cocktail used to treat the surface of beef that was contaminated (103CFU/g) *with E. coli* O157:H7 eliminated the bacterium from a majority of the treated specimens [13].
***Escherichia coli* O157:H7**	EcoShield™(formerlyE CP-100)	*E. coli* O157:H7 levels decreased by ~1–3logs, or were reduced below the limits of detection, on tomatoes, broccoli or spinach after treatment with a phage cocktail, while *E. coli* O157:H7 levels were decreased by ~1log when the phages were applied to ground beef [103].
***Escherichia coli* O157:H7**	EcoShield™(formerlyE CP-100)	A phage cocktail applied to experimentally contaminated lettuce and cut cantaloupe significantly reduced *E. coli* O157:H7 levels by up to 1.9 and 2.5 logs, respectively [104].
***Escherichia coli* O157:H7**	CocktailBEC8	At various temperatures (4,8,23and37◦C), the phage cocktail significantly reduced the level of *E. coli* O157:H7 on leafy green vegetables by ~2–4logs. The inclusion of an essential oil (trans-cinnamaldehyde) increased this effect [105].
***Escherichia coli* O157:H7**	EcoShield™(formerlyE CP-100)	The levels of *E. coli* O157:H7 were reduced by ≥ 94% and ~87% on the surface of experimentally contaminated beef and lettuce, respectively, after addition of the phage cocktail; however, the single treatment did not protect foods after recontamination with the same bacteria (i.e., phage biocontrol had no continued technical effect on the foods) [106].
***Escherichia coli* O157:H7**	EcoShield™(formerlyE CP-100)	After a 30 min phage treatment at both 4 and 10◦C, levels of *E. coli* O157:H7 decreased by > 2logs on leafy greens under both ambient and modified atmosphere packaging storage [107].
Escherichia coli	FAHEc1	Contamination of raw and cooked beef decreased by 2–4 logs at 5, 24 and 37◦C in a concentration dependent manner after phage application. The *E. coli* displayed regrowth at higher temperatures [108]
***Escherichia coli* O157:H7**	EcoShield™(formerlyE CP-100)	A phage cocktail was applied to lettuce by spraying and dipping. A larger initial reduction (~0.8–1.3 logs) in *E. coli* O157:H7 counts was observed after spraying. Dipping required submerging the lettuce for as long as 2min, and the initial reductions were not significant. After 1 day of storage at 4◦C, dipping in the highest concentration of the phage cocktail reduced *E.coli* by ~0.7 log [109].
Escherichia coli	EC6,EC9,EC11	Two*E.coli*strainswereeradicatedfromrawandUHTmilkaftertreatmentwit hathree-phagecocktailat 5–9◦Cand25◦C.Forathird*E. coli*strain, phage treatment eliminated the bacteria from UHT milk; however,afteraninitialreduction,regrowthoccurredintherawmilkafter144 or9hfor5–9◦Cand25 ◦C storage, respectively [95].
Escherichia coli, Salmonella, Shigella	EcoShield™(formerlyE CP-100), SalmoFresh™,ShigActiv e™	Phage cocktails were as effective as or more effective than chlorine wash at reducing targeted pathogenic bacteria from broccoli, cantaloupe and strawberries in samples containing a large amount of organic content. Combination of the phage cocktail and a produce wash generated a synergistic effect, i.e., higher reductions of bacteria [110].

Table 3
Phageproductsapproved for food safety applications

Company	PhageProduct	TargetOrganism(s)	Regulatory
FINK TEC GmbH (Hamm, Germany)	SecureShieldE1	*E. coli*	FDA, GRN 724 pending as of 19 March 2018
Intralytix, Inc. (Baltimore, MD, USA)	Ecolicide® (EcolicidePX™)	*E. coli* O157:H7	USDA, FSIS Directive 7120.1
	EcoShield™	*E. coli* O157:H7	FDA, FCN 1018;Israel Ministry of Health; Health Canada
Micreos Food Safety (Wageningen, Netherland)		*E. coli* O157:H7	FDA, GRN 757 pending as of 19 March 2018
Passport Food Safety Solutions (West Des Moines, IA, USA)	Finalyse®	*E. coli* O157:H7	USDA, FSIS Directive 7120.1

[103, 104, 106, 107, 109, 110].

VI. Potential Problems With Phages As Biocontrol Agents

6.1 Release of Endotoxins: Even though it looks unlikely that phagetherapy that has been purified results to relevant toxic side effects, vital concerns surrounds the potentially huge release of bacterial endotoxins after bacterial lysis which observations have been similarly made with the use of some antibiotics [111] as well as immune reactions to bacterial components including endotoxin present in crude phage lysates. Challenges with large amounts of bacterial endotoxins could lead to clinical breakdown of septic patients [112, 102]. However, [113] reported for two different E. coli phages fewer released endotoxins in vitro compared to β-lactams, while the phage-evoked endotoxin level was comparable to that evoked by amikacin [113].

6.2 Potential Risk of Anaphylaxis: Phages are members of microbial communities and are present in the environment as well as on and in the human body [114]. Despite this, therapy with phages requires a higher titre compared to their naturally occurring numbers. Moreover, the use of high phage titres in patients bears the theoretical risk of inducing extreme immune responses like anaphylaxis [115]. Although theoretically possible, anaphylaxis due to phage therapy has never been reported and does not seem to be a major concern in phage therapy [65].

6.3 Immune Response to Phages: Being composed of proteins and nucleic acids, phages in general are considered as innately non-toxic [65]. Nevertheless, there is evidence for non-specific immunomodulatory characteristics of phages, as well as stimulation of anti-inflammatory and phagocytic properties. Roach *et al*. reveal that the presence of neutrophils is necessary for phage therapy success against *P. aeruginosa*[116]. It is also possible that the human immune system may recognize phages as foreign antigens and produce phage-neutralizing antibodies depending on the application route [117]. In order to minimize the risk of side-effects due to impurities, it is necessary in at least parenteral application routes to use highly purified phage preparations.More scientific evidence is needed for a worldwide use of human phage therapy according to Western European medical standards. In the areas of immunological reactions following single or repeated phage application, further investigation is warranted, pharmacokinetics and dynamics and interaction with bacterial biofilms and commensal flora [118]

6.4 Activity against Intracellular Pathogens: Phages are unlikely to be able to actively enter eukaryotic cells. Therefore, phages are less effective against intracellular bacteria for example, *Mycobacterium tuberculosis*, as well as against intracellularly-surviving and persistent clones of extracellular bacteria, for example, *Acinetobacter baumannii*[115].

VII. Consumer Acceptance

Lately,consumershave progressively indicated a cold mind topurchasefoodstreated withantibiotics and chemical sanitizers or foods that are "genetically modified", The demand for organic foods and products produced locally, such as at local farmer's markets and CommunitySupportedAgriculture(CSA),has simultaneously beenontherise [119]. Thistrend portend wellforphage biocontrol, which offers agreen, non-chemical, and targeted antimicrobial approach for advancing the safety of foods. However,to purchase foods processed with unfamiliar techniquesmay be disinclined by the public, and the idea of "spraying viruses onto their food" could cause discomfort. It will be critical to provide education to the public and food processors, to explain the safety, efficacy, and ubiquity of bacteriophages for phage biocontrol to be more widely utilized [120].

Phages are the most abundant organisms on the planet with approximately 10^{31} particles existing (ten times that of the total global bacterial population) [121], and approximately 10^{15} phage particles populating the human intestinal tract [122]. Phages are part of the normal microflora of all fresh foods [123], and they have been isolated from a variety of foods, from fruits and vegetables to meat and dairy products, often in very high numbers, e.g., up to 1×10^9 PFU/mL in yogurt [124, 125]. Most friendlyenvironmental interventions available is likely to be phage biocontrolin previous reviews [126], it was estimated that if phages were applied at the maximum accepted amount (current approvals are for up to 10^7–10^8 PFU/g and for single phage product 10^9 PFU/g) to all the accepted food eaten by the average American in one day, the phages consumed would represent<0.2%ofthenumberofphagesalreadyinside thehumanintestinaltract. Thiscalculation is a gross overestimate, considering especially several GRAS approvals permit an application of up to 10^8 PFU/g (reducing the daily intake of phage to ~0.02% of the phage in the human intestinal tract). Also, this estimate assumes that;

- all possible food is treated
- all the phages applied survive the acidic pH of the stomach and make it into the small intestine (yet, when exposed to the acidic pH of the stomach, most of the phages are usually destroyed)
- the highest approved amount of phages is applied, and

- all the relevant food industries in the United States universally use phage biocontrol.

Briefly, when compared to naturally present phage populations, the number of phages added to the environment and introduced into the human intestinal tract as a result of phage biocontrol is negligible. In the first place, phages in all currently available commercial products (Table 2) are not genetically modified and originated from the environment, potentially even from foods, yet general public is often not aware of these facts. For further successful implementation of this promising approach, proper understanding of thesafe nature and ubiquity of lytic phages and the advantages and disadvantages of phage biocontrol by consumers and food processors alike will be critical. In at least one recent study, consumers appeared to be willing to pay more for bacteriophage-treated fresh produce after the science behind phage biocontrol and the advantages of this technique were explained to them [127].

VIII. Conclusion

Though some challenges remain, bacteriophage biocontrol is increasingly accepted as a safe and effective method to eliminate, or significantly reduce the levels of, specific bacterial pathogens from foods. In a growing number of countries, bacteriophage of commercial products are currently available and have been approved for use. At a variety of timepoints during food production, these products can be used to address contamination by specific bacterial pathogens, includingapplying to livestock animals before processing, spraying on produce, rinsing of food contact surfaces in processing facilities, and treatment of post-harvest food products, including Ready To Eat foods. Foodborne illnesses remain a constant threat, especially for individuals with weaker immune systems, e.g., children, the elderly, and pregnant women despite the progress made in improving the safety of our foods. To preventfoodbornepathogensfromreachingconsumers, bacteriophage biocontrol can serve as an additional tool in a multi-hurdle approach,andthismethodisespeciallypromisingunder circumstances when food processors strive to only remove the bacteria that may cause illness in humans while preserving the natural, and often beneficial, microbial population of foods.

IX. Recommendation

In the year 2017-2018, South Africa recorded a massive outbreak of Listeriosis due to *Listeria monocytogenes* associated with ready to eat processed meat products [128]. A possible approach to control this is the use of bacteriophages and strong surveillance system to facilitate prevention and early detection.

Acknowledgement

We would like to thank the Director of Africa Center of Excellence in Phytomedicine Research and Development, University of Jos, Plateau State, Nigeria, Prof. J. C. Aguiyi for the financial support and creating an enabling environment for this review work.

CONFLICT OF INTEREST

The authors has no conflict of interest to declare

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Ngene, Anayochukwu Chibuike,etal."Bacteriophages as Bio-control agent against Food-Borne Pathogen E. coli 0157:H7."*IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 15(2), (2020): pp. 23-36.