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Bacteriophage Therapy for Safeguarding Animal and Human Health: A Review

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Abstract: Since the discovery of bacteriophages at the beginning of the 19th century their contribution to bacterial evolution and ecology and use in a variety of applications in biotechnology and medicine has been recognized and understood. Bacteriophages are natural bacterial killers, proven as best biocontrol agents due to their ability to lyse host bacterial cells specifically thereby helping in disease prevention and control. The requirement of such therapeutic approach is straight away required in view of the global emergence of Multidrug Resistant (MDR) strains of bacteria and rapidly developing resistance to antibiotics in both animals and humans along with increasing food safety concerns incuding of residual antibiotic toxicities. Phage typing is a popular tool to differentiate bacterial isolates and to identify and characterize outbreak-associated strains of *Salmonella*, *Campylobacter*, *Escherichia* and *Listeria*. Numerous methods viz. plaque morphology, ultracentrifugation in the density gradient of $CsCl_2$, and random amplified polymorphic DNA (RAPD) have been found to be effective in detection of various phages. Bacteriophages have been isolated and recovered from samples of animal waste products of different livestock farms. High titer cocktails of broad spectrum lytic bacteriophages are usually used for clinical trial for assessing their therapeutic efficacy against antibiotic unresponsive infections in different animals. Bacteriophage therapy also helps to fight various bacterial infections of poultry viz. colibacillosis, salmonellosis and listeriosis. Moreover, the utility of phages concerning biosafety has raised the importance to explore and popularize the therapeutic dimension of this promising novel therapy which forms the topic of discussion of the present review.

Key words: Bacteriophage, phage therapy, treatment, animals, humans, antibiotic resistance, biocontrol, food safety

INTRODUCTION

Bacteriophages are termed as 'superbug' and are attractive tool for antibacterial therapy, biocontrol of bacterial contamination of foodstuffs, control of water- and food-borne pathogens, identification and differentiation of bacterial isolates, controlling environmental microflora, plant protection and especially for treating various infections of both humans and animals (Merril *et al*., 2003; Chinabut and Puttinaowarat, 2005; Greer, 2005; Carlton *et al*., 2005; Rees and Dodd, 2006; Skurnik and Strauch, 2006; Gaidelyte *et al*., 2007; Hagens and Loessner, 2007; Johnson *et al*., 2008; Abedon, 2009; Almeida *et al*., 2009; Balogh *et al*., 2010; Rakhuba *et al*., 2010; Waseh *et al*., 2010; Kotay *et al*., 2011; Pereira *et al*., 2011; Ahmad *et al*., 2012; Tabla *et al*., 2012; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2011, 2012a, 2013). During the last decade developed countries have shown trend towards reduction in antibiotic usage in animals due to its potential hazardous effects on human population after the consumption of livestock products (Dhama *et al*., 2013a). There are number of reports of increasing antibiotic resistance in animal pathogens of zoonotic importance viz., *Campylobacter* spp., *Escherichia coli*, *Staphylococcus* spp., *Salmonella* spp. and many other bacterial

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pathogens (Abhilash *et al*., 2009; Kumar *et al*., 2010, 2012b). Moreover, being in the close viscinity to human being particularly in developing countries or in the countries of third world, these infected animals and the contamination through them is most common source of transmission of these MDR strains to human being (Kumar *et al*., 2011, 2012a, b; Malik *et al*., 2012; Singh *et al*., 2013).

Rising antibiotic resistance in many clinically significant bacterial species coupled with a shortage of novel classes of antibiotics has created an urgent need for the development of alternative antibacterial agents. Seeing the emergence of antibiotic resistance against several bacterial pathogens and food safety concerns like residual effects of antibiotics in animal meat, meat products and milk, there is a growing interest in finding viable alternatives for disease prevention, control and growth-enhancing supplements. In these scenario new modalities of treatment viz. bacteriophages; avian egg antibodies and cytokines; probiotics and herbs and others are available now (Abhilash *et al*., 2009; Mahima *et al*., 2012). The bacteriophages in particular have been proposed as potential candidates to serve as an alternative to antibiotics in animal disease prevention and control. In treating drug-resistant bacterial infections (both in humans and their companion animals) it is particularly very effective (Chakravarthi and Balaji, 2010; Abedon *et al*., 2011; Dhama *et al*., 2011; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2011, 2012a, b; Dhama *et al*., 2013b).

Bacteriophages are viruses that subsist on bacteria and have proved to be the best biocontrol agents by lysing bacterial entities. A British bacteriologist, Twort (1915) appeared as first person to recognize these agents as viruses which infect bacteria, followed by D'Herelle (1917) who virtually for the first time coined the term bacteriophage for these, commonly called as phage and are considered as the magical viruses or superbugs. They are proved as best biocontrol agent, preventing water-borne, food-borne and drug resistant infections of bacterial origin as they specifically lyse the host bacterial cells (Greer, 2005; Borysowski *et al*., 2006; Gaidelyte *et al*., 2007; Hagens and Loessner, 2007; Johnson *et al*., 2008; Abedon, 2009; Balogh *et al*., 2010; Waseh *et al*., 2010; Pereira *et al*., 2011; Ahmad *et al*., 2012; Tiwari *et al*., 2012a). Phage therapy predated antibiotics by decades, but has been largely supplemented when antibiotics are available. In the current era of continued emergence of antibiotic resistance of various bacterial strains and food safety concerns like residual effects of antibiotics in animals and their food (milk, meat), there is a growing interest in finding viable alternatives for disease prevention and control (Garcia *et al*., 2008). Research on the application of bacteriophages in the recent past has focused on the treatment of enteric and respiratory infections in livestock and poultry and various food products of animal origin (Thiel, 2004; Abhilash *et al*., 2009; Ahmad *et al*., 2012; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2012a; Tiwari *et al*., 2013).

Recently, Food and Drug Administration (FDA) approved bacteriophages for direct addition to food as feed additives for human consumption and it has opened doors for the commercial production and million dollar market of bacteriophages. In the recent past research on the application of bacteriophages has focused to treat enteric and respiratory infections in livestock and poultry, and various food products including plants (Andreatti Filho *et al*., 2007; Abhilash *et al*., 2009; Balogh *et al*., 2010). However, improved approach is required to evaluate the efficacy of bacteriophage therapy in cases of different bacterial infections and the use of enzybiotics, lytic phage as well as non-lytic phage to specifically target the bacterial pathogens (Abhilash *et al*., 2009). In view of this search superbug therapy has been proved as a promising revitalized therapy. The lethality and specificity of phages for particular bacteria and a number of studies have indicated the applicability of bacteriophages in fighting various bacterial infections, both as prophylactics and therapeutic agents, particularly found useful in bacterial enteritis, respiration infections and combating bacterial pathogens viz., *Escherichia coli* and *Salmonella* spp.; *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*; *Staphylococcus aureus* and *Streptococcus pyogenes*; *Bacillus anthracis* and *Listeria monocytogenes*; *Campylobaeter jejuni* and *E. coli* and others (Capparelli *et al*., 2007; Abedon *et al*., 2011; Hermans *et al*., 2011). Thus, bacteriophages are much helpful in preventing food-borne and zoonotic bacterial pathogens and their full potentials need to be explored. Phage therapy is also being used to increase the shelf life of fruits, vegetables, meat and plants (Balogh *et al*., 2010). For treatment of infectious diseases, especially in the scenario of emerging antibacterial resistance in both medical and veterinary sciences a good role is expected to be played by novel therapy with these efficacious antibacterial agents. It is foresighted that phage 'the real conqueror of bacteria' will provide potential tool to face the crisis of antibiotic over use and is the best choice to replace antibiotics for sustainable livestock production and human welfare (Carlton *et al*., 2005; Capparelli, *et al*., 2007; Johnson *et al*., 2008; Tiwari *et al*., 2012a).

The present review reports the therapeutic potential and clinical efficacy of the bacteriophages in animals and humans and their utility in bicontrol and foodsafety issues.

ECOLOGY AND SOURCES OF PHAGES

Phages exist wherever bacteria occur sharing a common ecology with their respective bacterial hosts Studying the titer of phage in biosphere reflected these phages to be the most abundant entities in the biosphere with total number estimated from 10^{30} to 10^{32} (Duran *et al*., 2002; Sulakvelidze and Kutter, 2005; McLaughlin *et al*., 2006). Bacteriophages that are active towards pathogenic microflora are usually acquired from the material obtained from a given patient (urine, faeces, pus, etc). Bacteriophages are naturally found in the alimentary tracts of humans; animals including poultry as well as in foods, soil, water, sewage and associated environmental niches. Thus, for phages infecting the gut flora, municipal and farmhouse sewage is an excellent source. Bacteriophages can be relatively easily isolated from various sources. The best source of a given phage is material where its specific host is abundant because they share a common ecology with their bacterial hosts. The other alternative that gained further widespread acceptance is the isolation of virulent phage isolates from sewage waters (normally from the clinic) (Sundar *et al*., 2009; Tiwari *et al*., 2010; Tiwari *et al*., 2012a). Phages have been isolated at times from waste water; surface water or sewage. Those active on *Escherichia coli* B-4, *Salmonella*, *Aerobacter*, *Proteus*, *Serratia, Vibrio natriegens, Bacteriodes fragilis*; *Yersinia enterocolitica* and *C. jejuni)* and fecal material; polluted samples of water and sediments (Wais and Goldberg, 1969; Hankin, 1896; Bergh *et al.,* 1989; Carey-Smith *et al*., 2006; Jamalludeen *et al*., 2007). Phages are most abundant in the environment; titer being highest in biosphere (around 10^{30} and 10^{32}). Most of the workers stressed upon choice of appropriate host bacterium for optimum recovery of phages. There are reports that support the use of either *B. subtilis* and/or *E. coli* (Goodridge *et al*., 2003; Huff *et al*., 2003a; Muniesa *et al*., 2004; Sulakvelidze and Kutter, 2005). Result of initial screening by the turbidity reduction method indicate the possibility of recovery of phages to be maximum in waste samples from dairy cattle farm (90%), followed by buffalo farm (75%), pig farm (67%), goat farm (67%), poultry farm (50%) and least in duck rearing ponds (17%). Phages for different bacteria have been isolated from domestic sewage containing mammalian feces (cows, pigs and humans) along with enumeration of coliphages and *Salmonella* phages. Two distinct phages infecting *Salmonella* from the sewage with phage FGCSSa1 having the broadest host range infecting six of eight *Salmonella* isolates and neither of two *E. coli* isolates is quiet noteworthy. Isolation of *Salmonella* phages from swine effluent lagoons and so also abundance of coliphages in pig feces have also been reported (Alavidze *et al*., 2000; Klausa *et al*., 2003; Carey-Smith *et al*., 2006; McLaughlin *et al*., 2006; Jamalludeen *et al*., 2007; Tiwari *et al*., 2012a).

DETECTION OF BACTERIOPHAGES

Small number of phages in large volumes of water may be detected by qualitative enrichment procedures with considerable increase in the phage titer when enrichment protocol or filter adsorption-elution technology is followed (Sekaminova *et al*., 1998; McLaughlin *et al*., 2006). Numerous methods viz. plaque morphology; ultracentrifugation in the density gradient of $CsCl_2$ have been found to be useful especially to detect the phages of *Bacillus pumilus* and *B. subtilis*; *B. thuringensis* or *B. polymyxa* and even that of coliphages. Moreover, Random Amplified Polymorphic DNA (RAPD) pattern helps to identify morphological features of phages (viz. KH1, KH2 and KH3) of Enterotoxigenic *Escherichia coli* (ETEC) and *Lactobacillus plantarum* phage Ø JL-1 (Grabow, 2001; Goodridge *et al*., 2003; Huff *et al*., 2003a; Klausa *et al*., 2003; Lu *et al*., 2003; Sajjad *et al*., 2004; McLaughlin *et al*., 2006; Jamalludeen *et al*., 2007).

Phage typing and grouping of phages: Phage typing is a popular tool to differentiate bacterial isolates and is used in epidemiological studies for identifying and characterizing outbreak-associated strains of *Salmonella*, *Campylobacter*, *Escherichia* and *Listeria* but further evaluation regarding its efficacy is required (Parisien *et al*., 2008; Abedon and Thomas-Abedon, 2010; Ahmad *et al*., 2012). Electron microscopic studies of *Proteus*, *Bacillus* and T-4 bacteriophages; sewage coliphages along with morphotyping of bacteriophages of *Lactobacillus helveticus* have been conducted from time to time (Goyal *et al*., 1987; Grabow, 2001). Ten varieties of morphologically different phages have been classified into four different families; namely, Myoviridae, Styloviridae, Podoviridae and Microviridae; whereas on the basis of morphology and nucleic acid content additionally Microviridae, Inoviridae, Siphoviridae and Leviviridae are taken into consideration (Chopin *et al*., 1976; Ackermann, 2003).

BACTERIOPHAGES: FEATURES AND MECHANISM OF ACTION

These are tadpole-shaped microorganisms; their genetic material (DNA or RNA) is surrounded by a protein coat, a hollow protein tail and tail fibres; based on life

cycle are either lytic or temperate phages (Ackermann, 2012). Holin enzyme, which rapidly lyses the bacterial host cell and allows virion particles to further infect other bacterial cells during the course of multiplication and the mechanism can be exploited for therapeutic purpose (Courchesne *et al*., 2009; Fischetti, 2010; Tiwari *et al*., 2012a). Certain lysins (especially those of phages of Gram-negative bacteria) are capable of affecting bacterial cells by a mechanism completely independent of their enzymatic activity (Orito *et al*., 2004). Temperate phages integrate their genome into host-cell DNA as a prophage and can transfer virulence and other harmful genes from one bacterium to another by transduction. Narrow range phages are restricted to maximum of two bacterial species (Goodridge *et al*., 2003; Carey-Smith *et al*., 2006; Keen, 2012). Bacteriophages are species specific, self-perpetuating, self-limiting and eco-friendly in nature and can survive in the gastrointestinal environment of animals and can minimize the threshold level of infectous organisms such as *Salmonella*, *Shigella*, *Staphylococcus*, *Escherichia*, *Campylobacter* etc. Phage isolates which are initially isolated by using *B. subtilis* and *E. coli* have also been tested for lytic activity against more bacteria viz. *Staphylococcus aureus*, *Salmonella spp.* and *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Phage host range is not always genera restricted and phages could be of wide host range (Shasha *et al*., 2004; Bielke *et al*., 2007; Balasubramanian *et al*., 2007; Tiwari *et al*., 2012a).

FACTORS AFFECTING REPLICATION OF PHAGES

Several factors cells viz., pH, temperature, organic matter, relative number of host bacteria and phage, ionic concentration *etc.* promote replication of phages. Elevated temperature affects synthesis of DNA in bacteriophage Ø29-infected *Bacillus amyloliquefaciens* thereby effecting replication. Feces of warm blooded animals contain only Mid-Temperature (MT) and High-Temperature (HT) phages and titers of phages either in pure culture phage suspension or in naturally occurring phage suspensions are stable at (-70±10)°C and at (-20±5)°C, when protected with glycerol. The lipid-containing phage was insensitive to pH (5.7-8.0) but an increase in pH and calcium or magnesium ion concentration has moderate effect on enhancing detachment. Phage viability is maximum between pH 5 and 9 and all phages are completely inactivated at pH values of 3 and 11. Season also has impact on the replication of phages especially in case of host specific phages of *Salmonella typhimurium* and *Bacteroides fragilis* whose total number vary especially during summer season (Kinoshita *et al*., 1993; Brenner *et al*., 1999; Mendez *et al*., 2002; Jamalludeen *et al*., 2007; Lu *et al*., 2003).

IN VITRO AND *IN VIVO* STUDIES OF PHAGE THERAPY: MATTER CONCERNING CLINICAL AND MEDICINAL APPLICATIONS

Present period is designated as an era of increasing bacterial antibiotic resistance due to multi drug resistant microbes, thus there is renewed interest in the therapeutic applications of phages in the cure and treatment of infectious disease particularly of bacterial origin (Barrow and Sothill, 1997; Sulakvelidze *et al*., 2001). However, it was Delbrück and his coworkers who first time selected three of the seven virulent coliphages-T2, T4 and T6-from among early, largely "therapeutic" isolates for therapeutic use (Miller *et al*., 2003).

The careful study of the host range, lytic spectrum, cross resistance and other fundamental properties of the phage being used is a major factor in the reported successes of the phage therapy works. The findings of purified PlyG lysin (an *N*-acetylmuramoyl-l-alanine amidase) produced by gamma phage of *Bacillus anthracis* which effectively kill the bacterium (Schuch *et al*., 2002) boosted the scientific community to find out similar products. This also supported the probability for the development novel products from the known thousands of available bacteriophages that can target various cellular processes, inhibiting or killing their host bacteria (Miller *et al*., 2003).

Phage therapy in medical science: Treatment of bacterial infections of human occurs naturally when phage therapy is involved. Phages were first used in human medicine to treat *Staphylococcal* skin infections (Bruynoghe and Maisin, 1921). Several different phages of *Staphylococcus* (116); *Klebsiella* (42); *Proteus* (11); *Escherichia* (39); *Shigella* (30); *Pseudomonas* (20); *Salmonella* (1) have been successfully used to treat long-persisting suppurative fistula; septicemia and abscesses; respiratory tract suppurative infections and bronchopneumonia; purulent peritonitis and furunculosis in human. Therefore, in the current era of multidrug resistant pathogens phage therapy has been reported to be an important alternative to antibiotics. The complication due to release of endotoxin by gram negative bacteria and subsequent induction of fever and toxic shock can be prevented by using genetically engineered bacteriophages that becomes an interesting approach in human medicine. Phages effective against extracellular *Staphylococcus aureus* including methicillin resistant staphylococcal

strains have also been detected and named as bacteiophage (M^{Sa}). Such phages can prevent formation of abscess along with reduction of bacterial load of abscesses and thus are proved to be effective against both local as well as systemic *S. aureus* infections. (Dlopek *et al*., 1987; Mathur *et al*., 2003; Shasha *et al*., 2004; Qazi *et al*., 2004; Capparelli *et al*., 2007; Wright *et al*., 2009; Rhoads *et al*., 2009; Tiwari *et al*., 2012a).

Reports of success of phage therapy against the extracellular bacteria is abundant but against intracellular bacteria is scarce and only limited reports of *in vivo* studies are available elucidating the effects of phages against infections of *Brucella*, *Chlamydia* or *Mycobacteria*. Bacteriophage against *Mycobacteria* has been referred as mycophage or mycobacteriophage by certain workers and such phages have been isolated both healthy and diseased individuals. Studies have revealed that few *Mycobacteria* are susceptible to specific bacteriophages provided they are treated before their entry into the host cell even though it was initially opined that phages can not kill the intracellular bacteria. Phages may play a crucial role against rapidly growing non-pathogenic *Mycobacteria* but certain lysogenic strains of *Mycobacteria* have also been detected. Mycobacterial viruses such as AG1 and ph60 have been found to be lytic against BCG and *M. paratuberculosis* strain while V24 mycophage has shown sensitivity against rapidly growing *Mycobacteria* only (Pedulla *et al*., 2003; Sulakvelidze *et al*., 2001; Emery and Whittington, 2004; Graham, 2005; Verbeken *et al*., 2007).

Therapeutic phages are clearly different from classical chemical or molecular medicinal products (such as antibiotics) but they are certainly natural entities playing crucial role in the maintenance of equilibrium in bacterial populations in human and thereby must be considered more as evolving as well as interactive antibacterial products but not as stable conventional medicinal products. Thus, they can often be used synergistically with antibiotics required for sustainable therapy and must not be neglected (Comeau *et al*., 2007; Pirnay *et al*., 2012).

Phage therapy in veterinary field

In animals: Clinical applications of bacteriophages have focused aquaculture and various food products and could prevent food-borne and zoonotic bacterial pathogens (Soothill *et al*., 2004; Brussow, 2005; Carlton *et al*., 2005; Sheng *et al*., 2006; Capparelli *et al*., 2007; McVay *et al*., 2007; Johnson *et al*., 2008; Miller *et al*., 2010; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2012a, 2013). Bacteriophages are much in demand during the current era of the emergence of antibiotic resistance against several bacterial pathogens, and food safety concerns like residual effects of antibiotics in animal meat, meat products and milk and have got enormous therapeutic potential (Hermoso *et al*., 2007). Bacteriophages are administered via intramuscular (i/m) injection, aerosol spray and oral treatment.

Phage therapy has regained its original importance during the last two decades (Lu *et al*., 2003; Sajjad *et al*., 2004; McLaughlin *et al*., 2006; Ahmad *et al*., 2012). Phage treatment was found more effective than using antibiotic such as tetracycline; streptomycin; ampicillin and trimethoprim/sulfafurazole. A number of potential candidate phages are waiting for approval to be used for therapeutic purpose especially against burn injuries and post burns; chronic wound infections as well as purulent peritonitis and septicemia. Even if the administration of the phage is delayed (until signs of disease appear) protection can be achieved as the phage can multiply in the blood. Intra-muscular inoculation of phage delay the appearance of *E. coli* (given orally) in the blood and lengthen life-span in newly borne calves which are colostrums deprived. For treatment, a phage 'Cocktail' (mixture of few different phages) collectively providing a wider antibacterial range or the use of a single phage with a broader antibacterial spectrum proved to be most effective. Suppurative wound infections and gastro-enteritis, sepsis as well as dermatitis, empyema and pneumonia caused by pathogens viz. *Staphylococcus* and *Streptococcus*; *Klebsiella* and *Pseudomonas*; *Escherichia* and *Proteus*; *Shigella* and *Salmonella* species can be treated (Tiwari *et al*., 2012a, 2013).

Administration of phages orally, topically in animal models (mice, guinea pigs and livestock) is useful to demonstrate efficacy against *E. coli*; *Acinetobacter, Pseudomonas* and *Staphylococcus* species. The literature also reveals use of coliphages for successful treatment in toxigenic *E. coli* and *Salmonella* infections. A lytic bacteriophage has been used to prevent septicemia and meningitis like infection in calves caused by *E. coli* (Summers, 2001; Ahmad, 2002; Bull *et al*., 2002; Huff *et al*., 2002; Goode *et al*., 2003; Brussow, 2005; O'Flynn *et al*., 2004; Toro *et al*., 2005; Atterbury *et al*., 2007). Phage therapy has been found to be essential in chronic antibiotic resistant *Pseudomonas aeruginosa* ear infections in pet dogs that have not responded to conventional therapy by focusing on local and other than systemic infections (Soothill *et al*., 2004; McVay *et al*., 2007). Chronic suppurative abscesses, which are refractory to antibiotics, are very frequent conditions reported to the Veterinary Hospitals. It is opined that suppurative chronic abscess generally get heavily

infected with common pus forming bacteria. Such wounds provide favourable micro-environment for propagation of sensitive phages. Resultant effect shall be complete removal of pathogens from wounds leading to cent percent recovery of wound. Thus application of lytic phages as single dose may prove to be a successful therapy for treatment of suppurative chronic abscesses. Phages are also helpful in treating enteric and respiratory infections in humans as well as livestock. Phage treatment has been suggested as an intervention strategy for reducing number of *Salmonella typhimurium* in pigs and checking their rapid dissemination (Weber-Dabrowska *et al*., 2000; Lee and Harris, 2001; Sulakvelidze *et al*., 2001; Summers, 2001; Duckworth and Gulig, 2002; Mathur *et al*., 2003; O'Flynn *et al*., 2004; Sajjad *et al*., 2004; Brussow, 2005; Tanji *et al*., 2004 and 2005; Garcia *et al*., 2008; Gyles, 2008; Ahmad *et al*., 2012).

In poultry: A number of studies have indicated the applicability of bacteriophages (both prophylactically and therapeutically) in fighting various bacterial infections of poultry viz., *Escherichia coli*; *Salmonella enteritidis*, *Salmonella typhimurium* and *Salmonella* Gallinarum; *Campylobacter jejuni* and *Campylobacter coli*; *Listeria monocytogenes* that are responsible for colibacillosis, salmonellosis and listeriosis, respectively and thus prevent morbidity and mortality in chickens. Two bacteriophages isolated from wastewater and poultry faecal samples, namely EC-Nid1 and EC-Nid are shown to be highly effective against O1, O2 and O78, the predominant *E. coli* serogroups/strains. Phages can be used to significantly reduce the caecal colonization of *S. enterica* serotype *enteritis* and *typhimurium* in commercial broiler chickens. Administration of 10^4 pfu of phage AB2 to newly hatched chicks cause decrease in the number of *S. typhimurium* in croup and in the small intestine and caeca respectively. Combination of bacteriophages isolated from free-range chickens may be efficacious in reducing the concentration of *Salmonella enterica* serovar Enteritidis phage type 4 (*S. enteritidis* PT4) in the caeca of broilers, therefore reducing contamination of poultry products (Fiorentin *et al*., 2005; McPeake *et al*., 2005; Andreatti Filho *et al*., 2007; Atterbury *et al*., 2007; Donoghue *et al*., 2007; Jamalludeen *et al*., 2009; Oliveira *et al*., 2009). A multivalent bacteriophage cocktail (INT-401) has been reported to be effective for controlling necrotic enteritis of broiler chickens, caused by *Clostridium perfringens* with improvement in weight gain and feed conversion ratios (Miller *et al*., 2010). In birds carrying bacteriophages, the recovery of *Campylobacter* and the number of their strains has been reported to be reduced (Atterbury *et al*., 2005). Applying bacteriophages to chicken skin has revealed that a high titre of bacteriophages (10^7 pfu mL^{-1}) significantly reduced the numbers of *Campylobacter* isolated (Atterbury *et al*., 2003a, 2005; Goode *et al*., 2003; Connerton *et al*., 2008). Phage therapy, like with two candidate phages CP8 or CP34, for *C. jejuni* in broiler chickens has been employed for both preventative and therapeutic purposes (Loc Carrillo *et al*., 2005; Wagenaar *et al*., 2005, 2006; Loc Carrillo *et al*., 2007). Administration of bacteriophages like phage R- active and others decrease and/or eliminate *E. coli* infection and its various disease manifestations like septicemia, airsacculitis in birds (Barrow and Sothill, 1997; Huff *et al*., 2002; 2003a, b, c, 2004, 2005, 2006; Sajjad *et al*., 2004; Jorgensen *et al*., 2002; Xie *et al*., 2005; Sheng *et al*., 2006; Johnson *et al*., 2008; Oliveira *et al*., 2009; Lau *et al*., 2010; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2012a).

Large/high numbers of bacteriophages can successfully reduce the levels of *Salmonella* on processed poultry (broiler and turkey carcasses). Application of lytic phages has been found very effective in reducing *Salmonella* and *Campylobacter* contamination of chicken skin even resistant to antibiotics and can be helpful in providing safer poultry meat at processing and/or packaging (Goode *et al*., 2003; Atterbury *et al*., 2005; Higgins *et al*., 2005, 2010; Atterbury *et al*., 2007; Bielke *et al*., 2007; Borie *et al*., 2008; Bishop-Hurley *et al*., 2010; Carvalho *et al*., 2010; Connerton *et al*., 2011; Tiwari and Hirpurkar, 2011).

Listeria phages have been isolated with a wide host range, including multiple serotypes of *L. monocytogenes* and other *Listeria* spp. (Leverentz *et al*., 2003, 2004; Carlton *et al*., 2005; Kim *et al*., 2008). Bacteriophage therapy is a valuable option for controlling *Listeria* in undercooked poultry products. Recently, the FDA has permitted bacteriophages preparation as an anti-listerial agent for *L. monocytogenes* in RTE meat and poultry products and control on both raw and ready-to-eat food products (Soni *et al*., 2010). The presence of bacterial pathogens like *Salmonella*, *E. coli*, *Listeria* and *Campylobacter* in undercooked poultry is implicated as the natural source of human infection, for which bacteriophage therapy is a valuable option. Again use of phages in combination with competitive exclusion to reduce *Salmonella* from infected chicken have been investigated by developing a 'Cocktail" of distinct phage (i.e., phage showing different host ranges and inducing different types of plaques on *Salmonella typhimurium* cultures) and tested it *in vitro* as well as *in vivo*. Results indicate a protective effect of *Salmonella* specific phages against *Salmonella* colonization of experimentally infected chickens. Phages specific for various *Salmonella*

spp. *in vitro* could thus reduce the incidence of *Salmonella* recovery on processed broiler and turkey carcasses and can effectively reduce the levels of *Salmonella* on processed poultry (Fiorentin *et al*., 2004; Higgins *et al*., 2005, 2010; Huff *et al*., 2005; Toro *et al*., 2005; Atterbury *et al*., 2003a, b, 2007; Bielke *et al*., 2007; Borie *et al*., 2008; Johnson *et al*., 2008; Berge and Wierup, 2012; Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2012a).

Administering phages to poultry via food, water or aerosol spray can be successful on a commercial scale. Doses vary from 10^6 to 10^8 pfu mL^{-1} or higher.

In aquaculture/fishes: Many important bacterial diseases are found associated to fishes and other aquatic animals and most common among them are infection of *Aeromonas salmonicida*, *Aeromonas liquejaciens*, *Aeromonas hydrophila*, *Aerococcus viridans*, *Hemophilus piscium, Pseudomonas species, Salmonella*, *E. coli*, *Listeria* and *Campylobacter* and *Pasteurella piscicida* along with vibriosis and mycobacteriosis of several species of Pacific salmon. For these pathogens phages have been reported against most of these bacteria (Alavidze *et al*., 2000; Ahmad, 2002; Chibani-Chennoufi *et al*., 2004; Emery and Whittington, 2004; Connerton *et al*., 2008). A large number of phages have been reported in aquatic environment (Bergh *et al*., 1989). However, observations regarding the phage specific to *Pseudomonas plecoglossicidia* (a fish pathogen) (Park *et al*., 2000) and bacteriophage Listex P100 for the reduction of *Listeria monocytogenes* on the surface of fresh channel catfish fillets (Soni *et al*., 2010) as potential candidates for disease control require special mention.

EMERGING ANTIBIOTIC RESISTANCE AND BACTERIOPHAGE THERAPY-AN ALTERNATIVE TO ANTIBIOTICS

Antibiotics have saved millions of human and animal lives and augmented food production many fold to meet the demands of hunger worldwide. However, nowadays, antimicrobial resistance is becoming a serious problem worldwide (Duckworth and Gulig, 2002; Gyles, 2008). Bacteria undergo many drastic changes to survive the periods of starvation which increases their resistance to a variety of environmental insults (Kolter, 1992). Antibiotics have been so overused or misused in medicine and as growth promoters in farm animals nowadays that many potentially pathogenic bacterial species are becoming resistant to them. The natural ability of pathogens to develop resistance to every antibiotic is not only a threat to animal health but also leads to accumulation of antibiotic residues in livestock products, which causes residual toxicity in food animals and various side effects. Consumption of such products created hazardous threat to human population particularly because of the concomitant increase in immunosuppressed patients (Sulakvelidze *et al*., 2001).

Now-a-days, antibiotic resistance strains of different bacteria are emerging worldwide due to the non-judicious use of antibiotics in food animals and human beings and resistant mechanisms adapted by various bacteria (Duckworth and Gulig, 2002; Acar and Moulin, 2006; Gyles, 2008; Tiwari *et al*., 2012a), which is a major cause of delayed wound healing. On the basis of antibiotic sensitivity test it has been found that strains of *Pseudomonas aeruginosa, E. coli* and some other bacteria isolated from the wounds of animals are resistant to various antibiotics. *In vitro* studies reveal that resistant strains of bacteria are sensitive to phages in the laboratory. These findings are in agreement to the observations made by several other workers (Ahmad, 2002; Soothill *et al*., 2004). Effectiveness of phage therapy in combating bacterial infections which do not respond to treatment with the available antibiotics have been recorded (Sulakvelidze *et al*., 2001; Inal, 2003; Thiel, 2004; Huff *et al*., 2005; Johnson *et al*., 2008; Parisien *et al*., 2008; Abhilash *et al*., 2009; Fischetti, 2010; Chan and Abedon, 2012; Berge and Wierup, 2012; Tiwari *et al*., 2013). Commercial production of phage preparations is advancing and various phage products to treat certain bacterial infections are now available and applications and dimensions of bacteriophages in combating bacterial infections in animals is increasing nowadays (Summers, 2001; Thiel, 2004; Borysowski *et al*., 2006; Johnson *et al*., 2008; Almeida *et al*., 2009; Waseh *et al*., 2010; Pereira *et al*., 2011; Tiwari *et al*., 2012a). Thus, phage therapy can be very effective in certain conditions and has some unique advantages over antibiotics particularly in cases of Multidrug-resistant (MDR) pathogenic bacteria and also phages do not damage the normal microflora, are comparatively safer as have minimum side effects and are cost-effective and thus have been proposed to be used as an alternative therapy to antibiotics in animal disease prevention in future (Sulakvelidze *et al*., 2001; Thiel, 2004; Huff *et al*., 2005; Inal, 2003; Merril *et al*., 2003; Johnson *et al*., 2008; Parisien *et al*., 2008; Fischetti, 2010; Ahmad *et al*., 2012; Berge and Wierup, 2012; Chan and Abedon, 2012).

CONCERNING BIOCONTROL AND BIOSAFETY

Biocontrol of *E. coli* O157 with O157 specific bacteriophage has shown that O157:H7 infecting phages effectively kill EDL 932, but only aerobically thus, these

phages are inappropriate for use in the anaerobic gut. They also stated that virulent O157 antigen specific phages could play a role in biocontrol of *E. coli* O157:H7 in animals. A therapeutic trial concerning suppurative bacterial infections caused by multidrug resistant bacteria of different species with specific phages has confirmed the high effectiveness of phage therapy in combating bacterial infections which do not respond to treatment with the available antibiotics. Quantitative microbiological procedures to explore the therapeutic potential of phages *in vitro* (the Phage Replication Assay or PRA) as well as *in vivo* have been developed. Using the *E. coli* KI mouse thigh infection model and applying treatments of phages or Streptomycin the microbiological efficacy of different phages in preventing mortality has been demonstrated by some workers. Higher concentration of mixed *Bacillus anthracis* phages have been found to inhibit subsequent growth of bacteria when sprayed on *B. anthracis* spore (Kudva *et al*., 1999; Weber-Dabrowska *et al*., 2000; Bull *et al*., 2002; Walter, 2003). Four T-4 coliphages of *E. coli* with broad host range when compared of *in vitro* and *in vivo* for bacteriolytic activity in mice have revealed that the minimal oral dose for consistent fecal recovery is as low as 10^3 PFU/mL of drinking water. Phages added to the drinking water efficiently lyse *E. coli* strains recently introduced into the intestine of conventional mice and traced as ampicillin-resistant colonies similar to an *in vitro* phage susceptible *E. coli* strains freshly inoculated into axenic mice. Normal *E. coli* gut flora of conventional mice is merely affected by oral phage application despite the fact that majority of the murine intestinal *E. coli* colonies are susceptible to the given phage cocktail *in vitro*. Cocktail of 3 bacteriophages when exploited as biocontrol agent to eliminate the pathogen *E. coli* O157:H7 have indicated that the phage cocktail completely eliminate *E. coli* O157: H7 from the beef meat surface. For rapid and effective prevention of pathogenic *E. coli* in poultry a mixture of bacteriophages are considered to be biosafe and thus can prevent intestinal diarrhea; thereby decreasing the death rate and facilitate weight gain (Chibani-Chennoufi *et al*., 2004; O'Flynn *et al*., 2004; Tanji *et al*., 2004, 2005; Li *et al*., 2012).

Phages that are characterized by a narrow host range are limited in terms of risk of dissemination (particularly when there is accidental release in the environment). Under such circumstances use of natural phages having a narrow range of host or phages genetically modifying in order to infect only specific laboratory strains is proved to be helpful. It is possible to determine the adequate containment level due to examination of the biological risk in relation to use of bacteriophages to protect health of human against the identified risk. Manipulation of phage M-13 by the use of a non-pathogenic bacterial strain (laboratory strain of *E. coli* K12) requires only biosecurity level (BSL) – 1 facility whereas manipulation involving the same phage M13 in an activity that involves pathogenic *E. coli* O157: H7 requires BSL-2 (Clark and March, 2004; Verheust *et al*., 2010).

CONCLUSION AND FUTURE PERSPECTIVES

Bacteriophages have been proven to be valuable tools in the fight of mankind and animals against diseases, and require a multi-dimensional approach. Moreover, the usefulness of bacteriophages in the paradigms of genetics and biochemistry is beyond expectation. The predominance of phages is highest in deeper layer of waste water tank of cattle farm and lowest in duck rearing ponds; cent percent recovery being observed when the samples are from chronic wound infections or associated with multi-drug resistant bacteria. Phage isolation in *B. subtilis* or *E. coli* followed by cocktail preparation is important from the therapeutic point of view. Interestingly phages have the potential to control zoonotic pathogens as well that show great promise to prove them as valuable alternatives to traditional antimicrobials. Prevention and treatment of infections and injuries along with food safety issues by bacteriophage therapy may be feasible very practically in the near future. The particular superbug (bacteriophages) is a very promising revitalized therapy and advanced approach is required to test its efficacy in cases of different bacterial infections. There is a need to investigate the use of phage in a wide range of infections with the increasing incidence of antibiotic-resistant bacteria and a deficit in the development of new classes of antibiotics to counteract them. Clearly the time has come to look more carefully at the potential of phage therapy, both by strongly supporting new research and by scrutinizing the research already available. Valuable contribution to food safety and public health along with effective biocontrol of pathogens is possible when bacteriophages therapy is employed. This ultimately results in social benefit without causing any harm to human health. These double-edged entities certainly need to be explored further to overcome the hurdles faced in employing them in health science both therapeutically and prophylactically. But major drawback associated with bacteriophages therapy lies in the insufficiency and difficulty as far as funding related to patency of this particular entity is concerned which is a proven lengthy and complex process. Newer Food and Drug Administration (FDA) adopted policies are therefore required to make bacteriophages therapy successful and popular. Influence of genetically modified phages over the

balance of the ecosystem by the process of disseminating new genetic traits when released into the environment is another matter of concern and must not be overlooked. It is thereby likely that in the near future these efficacious antibacterial agents will play a good role in both medical and veterinary sciences (especially in the scenario of emerging antibacterial resistance) for treatment of infectious diseases.

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