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REVIEW ON BACTERIOPHAGE THERAPY: RENEWED APPROACH FOR MANAGEMENT OF BACTERIAL INFECTION

Dubale Beyene[1], Sena Ayalow[1,] Bereket Yonas[2*], Omer Idris[2*]
[1] Department of Veterinary Science, College of Agriculture and Natural Resources, Jinka University, Ethiopia
[2*] College of Veterinary Medicine, Jigjiga University, Ethiopia
Corresponding Author: Dubale Beyene
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Abstract

Bacteriophages (phages) are viruses that infect and multiply in host bacteria and archaea. They are exceptionally diversified, abundant, and extensive. Phages were discovered just over a century ago and have been used to treat bacterial infections in humans and other animals since the 1919s. This seminar paper examines the usage of bacteriophages over time, their comparative benefits and drawbacks, and their application as a therapeutic tool in animals. Phage therapy is the use of lytic bacteriophages as a treatment against bacterial infections. It was frequently utilized in the pre-antibiotic era until large-scale antibiotic manufacture began. Today, the rising antibiotic resistance dilemma has revitalized bacteriophage therapy.

It has been offered as a possible alternative to antibiotics in the treatment and prevention of human and animal diseases. Its benefits include the fact that it does not harm natural microflora, is relatively safe, and has a positive effect on antibiotic resistance bacteria. Its main disadvantages are a limited host range and the potential of pathogenic gene transmission. Phage therapy in animal production has been debated in veterinary medicine for decades. Several investigations and clinical trials have supported the use of phages as a therapeutic technique for bacterial illnesses in animals. In poultry, swine, cattle, and fish, phage therapy produced good outcomes in terms of lowering mortality, clinical severity, and tissue-level bacterial counts.

It found that phage therapy has a promising outcome for the treatment of bacterial infections in both human and veterinary medicine. However, various obstacles must be resolved before lytic phages may be widely used for therapeutic purposes. To fully benefit from bacteriophage therapy, well-organized research and significant scholarly efforts are required.

Keywords: Antibiotic resistance, Bacteriophages, Pathogenic bacteria, Phage therapy,Virus

Introduction

Antimicrobial resistance (AMR) is an increasingly serious threat to human and animal population in this scenario. The problem is so serious that treatment of infectious diseases with antibiotics is becoming critically challenging and large number of patients dies annually from untreatable infections (Levy and Marshal, 2004). AMR also has a considerable economic impact: extra hospital costs and associated productivity losses. Looked for huge loss of life and the consequent economic loss and the situation is about to deteriorate even further, as there are only a few drugs left to treat multidrug-resistant bacterial strains led to an interest in discovering new therapeutic tools that allow replacing or complementing antimicrobials when combating bacterial diseases (Magoriakos *et al*., 2012).

Various modalities have been made to address the problem. These range from the more prudent use of existing antibiotics to the implementation of different antibacterial alternatives such as immune modulators, vaccines, avian egg antibodies, probiotics, and bacteriophage therapy (Brackman et al., 2011). Bacteriophage therapy seems to be promising and sustainable in the long term and implementable in the near future. Indeed, the use of bacteriophages to kill specific bacterial pathogens without harming the majority of the commensal bacteria has received increasing attention during the past decade (Sulakvelidze et al., 2001).

Bacteriophages are viruses that infect and replicate within host bacteria and archaea (Lyon, 2017). It has relatively simple structures composed of proteins (60%) that encapsulate a DNA or RNA genome (40%). Phages are among the most abundant entities in the biosphere. It has been estimated that there are more than 10^31 population on the planet with a total weight of 10^9 tons. They are ubiquitously distributed in environments populated by bacterial hosts, including soil, water, air, and the intestines of humans and other animals. Phages were usually classified into 19 families, over 140 genera, and more than 5300 types of phage species (Korotyayev and Babichev, 2002). Phages can also be divided into lytic phages and temperate phages based on whether or not their genome is integrated into the bacterial genome (Bao et al., 2018).

Phage therapy is the therapeutic use of phages to treat pathogenic bacterial infections. It was developed and widely used for the treatment of bacterial infection in human medicine, veterinary medicine, and agriculture between 1920 and 1940 until the first large-scale production of the antibiotic (Williamson et al., 2017). Nevertheless, research on phages and their medical applications continued particularly in the former Soviet Union and Eastern Europe. More recently, with the emergence of multiple antibiotic-resistant bacteria, the interest in phage therapy was renewed. Phage therapy has been proposed as a potential candidate to serve as an alternative to antibiotics in the control and prevention of human and animal diseases (Sulakvelidze et al., 2001).

The main advantage of phages is their specificity for target bacteria which reduces the damage to normal flora of the host greatly. Replication at the site of infection is another advantage of phages. They are safe with no or fewer side effects. After their administration phages can dissipate very quickly throughout the body reaching almost every organ and increasing in number whenever host bacteria are present (Clark and Marc, 2006). Bacterial resistance to phages, although likely to arise, should not be a major concern, certainly compared with bacterial resistance to antibiotics. This is because phages grow exponentially, essentially shadowing the bacterial growth and thereby mutating at the same rate due to the plethora of phages, there will certainly be a species that can attack mutated and resistant bacteria to prevent the escape of bacteria and its critical tools to combating antibiotic resistance (Dabrowska et al., 2005)

An increase in bacterial resistance to many antimicrobials has been observed, becoming a subject of global concern in human and veterinary medicine, and led to an interest in discovering new therapeutic tools that allow replacing or complementing antimicrobials when combating bacterial diseases and mitigating antimicrobial resistance crisis. Bacteriophages and viruses that infect and lyse bacteria are among these therapeutic tools. It was widely used before the advent of antibiotics and currently attracting the interest of the international scientific community (Boerlin, 2010). Therefore, this seminar paper was done with the objective of:

- To highlight features of bacteriophages
- To provide an insight into bacteriophage therapy, as an alternative to antibiotics and a tool for the mitigation of antibiotic resistance

2. LITERATURE REVIEW

2.1. Bacteriophage Definition and Discovery

Bacteriophages (or phages) are viruses that infect and replicate within host bacteria and archaea. The viruses of Kingdom Bacteria were first described as invisible entities capable of destroying bacterial cultures and would remain infectious even after suspensions were passed through filters designed to remove bacteria. Since the action of bacterial viruses resembled the eating of bacterial cultures, the word “phage”, which means to eat or devour in Greek, was chosen to describe this phenomenon (Dewangan et al., 2017).

Since ancient times, reports of river waters having the ability to cure infectious diseases have been documented, such as leprosy. In 1896, Ernest Hanbury Hankin reported that something in the waters of the Ganges and Yamuna rivers in India had marked antibacterial action against cholera and could pass through a very fine porcelain filter (Summers, 1999). In 1915, British bacteriologist Frederick Twort discovered a small agent that infected and killed bacteria. He believed the agent must be one of the following: a stage in the life cycle of the bacteria, an enzyme produced by the bacteria themselves, or a virus that grew on and destroyed the bacteria. Independently, French-Canadian microbiologist Félix d’Hérelle announced on 3 September 1917, that he had discovered "an invisible, antagonistic microbe of the dysentery bacillus". D'Hérelle called the virus a bacteriophage. It was D’Hérelle who conducted much research into bacteriophages and introduced the concept of phage therapy (Keen, 2012)

2. 2. Ecology and Source of Bacteriophage

Bacteriophages are found in almost all environments on Earth, ranging from soil, sediments, water (both river and seawater), and in/on living or dead plants/animals. Essentially, phages can be isolated from almost any material that will support bacterial growth. The estimated global phage population size is extraordinarily high (Parisien et al., 2008). It has been established that the population number of phages in aquatic systems lies within the range of 104 to 108 virions per ml and about 109 virions /g in the soil, 2 with an estimated total number of 1032 bacteriophages on the planet (Hanlon, 2007).

The production and distribution of phage are dependent on host concentration. The phage populations can grow faster when there is a greater density of susceptible bacteria. Generally, the virus-to-bacterium ratio falls between 3 and 10, depending on the nutrient level (Brüssow and Kutter, 2005). The consequence of phage lysis not only reduces the productivity of bacterial populations but also delays the ecosystem nutrient cycling and energy flow (Abedon, 2006)

2.3. Bacteriophage therapy

2.3.1. Definition Bacteriophage Therapy

Phage therapy is the therapeutic use of bacteriophages to treat pathogenic bacterial infections (Brüssow, 2005). Phage therapy may be defined more broadly than just the application of phages to human and animal bodies to combat bacterial disease. Indeed, at its most inclusive phage therapy represents the application of specific phages, which are pathogens of bacteria to selectively reduce or eliminate susceptible bacteria from natural environments, bodies of humans, animals, and artificial environments. In other words, phage therapy is simply another form of biological control the use of one organism to suppress another; and like other biological controls (Sulakvelidze and Morris, 2001)

2.3.2. Bacteriophage therapy mode of action and safety profile

Despite the large number of publications on phage therapy, there are very few reports in which the pharmacology of therapeutic phage preparations is delineated. The job of antibacterial, as expressed in terms of pharmacodynamics, is to kill or at least prevent the replication of one or more bacteria while not excessively harming the so-treated patient (Harper, 2006).

Antibiotics possess a wide array of mechanisms of action for example, penicillin inhibits cell wall formation while quinolones inhibit DNA gyrase and topoisomerase in bacteria As for their bactericidal activity, therapeutic phages were assumed to kill their target bacteria by replicating inside and lysing the host cell via a lytic cycle. However, subsequent studies revealed that many therapeutic phages may act via a similar cascade; however, it is also possible that some therapeutic phages have some unique yet unidentified genes or mechanisms responsible for their ability to effectively lyse their target bacteria. For example a group of authors from the EIBMV identified and cloned an anti-Salmonella phage gene responsible, at least in part, for the phage's potent lethal activity against the Salmonella enterica serovar Typhimurium host strains (Harper, 2006; Leitenberg, 2001)

The most important aspect of phages as antibacterials, other than their ability to kill bacteria, is their low toxicity. This low toxicity is a consequence of phage composition which for tailed phages is almost entirely protein and DNA. Phage interaction with the body's metabolism, such as that associated with the stomach, liver, and various aspects of the animal immune system can readily result in the degradation of phage virions However, unlike the metabolic decay of certain drugs, phage degradation does not result in the production of toxic byproducts. In addition, intact phages are not highly effective at interacting with other aspects of the body's metabolism such as in terms of specifically binding to or otherwise manipulating body tissues (Merril, 2008).

Furthermore, the body is routinely exposed to large numbers of endogenous phages meaning that the therapeutic application of phages is not qualitatively outside of the normal body experience (Gorski and Weber-Dabrowska, 2005) An exception to this relative safety could be anaphylactic immune-system responses to the proteins associated with phage virions, though even here reactions appear to be rare, plus mild when they do occur (Sulakvelidze and Kutter, 2005). Also, phages can be chosen and/or purified such that they are minimally associated with virulence factors, such as endotoxins or exotoxin-encoding genes (Waldor et al., 2005)

2.3.3. Bacteriophage Commercial Product and Legal Status

Phages are not specifically classified as living or chemical agents in any national medicinal legislation. This considerably complicates the regulation of phage therapy clinical trials and commercializing phage products (Fauconnier, 2017). Several clinical trials and case studies known to use bacteriophage therapy have been carried out under different jurisdictions. Individual countries have their regulators, and levels of regulation can be highly variable. (Verbeken et al., 2007)

The European Medicines Agency (EMA) considers bacteriophages as biological agents. Although bacteriophage therapy falls under the existing European regulatory framework on biological medicinal products the directive does not fully cover aspects specific to bacteriophages. Products such as vaccines (some of which are live viruses) that do not have specific regulatory guidelines have been approved by EMA. In the US, similar to the situation in Europe, no bacteriophage therapeutics guidelines for human use have been published by the Food and Drug Administration (FDA). Nevertheless, bacteriophage applications are handled by the Division of Vaccines and Related Product Applications (Verbeken et al., 2007; WMA Declaration of Helsinki, 2008)

The FDA currently recognizes commercial bacteriophage preparations against common bacterial pathogens such as Listeria monocytogenes and E. coli as safe and approves their use in food consumed by humans. The first approved food safety-related bacteriophage product was ListShield™ (LMP-102™), from Intralytix Inc, a phage cocktail that targets L. monocytogenes contaminants on ready-to-eat (RTE) foods containing meat and poultry products (Bren, 2007). Similar food safety applications and other nonhuman applications in the agricultural, animal husbandry, veterinary, and diagnostics sectors appear to be progressing well with an increasing number of products becoming available. Such products include AgriPhage, BioTector, EcoShield, Finalise, ListShield, and LISTEXTM P100L (Monk et al., 2010; Ryan et al., 2011).

2.4. Advantage and Draw Back Bacteriophage Therapy as Compared to Antibiotic

2.4.1. Potential advantage of bacteriophage therapy

Phage therapy, like any other therapeutic method, has advantages and disadvantages mainly related to antibiotic therapy. Among the advantages, the following are described:

1. Exclusively bactericidal capacity: bacteria that have been successfully infected by lytic phages are unable to regain viability. In contrast, few antimicrobials have bacteriostatic action only, and as a result, they may allow the evolution of bacterial resistance (LocCarrillo and Abedon, 2011).

2. Minimal effects on normal microflora: because of their close host specificity, which may include the ability to infect a few strains or bacterial species, more rarely, the ability to infect more than one genus, closely related to each other. In contrast, many antimicrobial chemicals that possess a wide spectrum of activity are likely to generate superinfections (Loc-Carrillo and Abedon, 2011).

3. Reduced potential to induce bacterial resistance: due fact that bacteriophages could have an improved efficacy as compared with antibiotics provides the greatest hope for the future. Regarding this subject, antibiotics have a clear limitation because they are stable, immutable chemicals and therefore are unable to adapt to bacterial mutations (Carlton, 1999)

4. Lack of cross-resistance to antibiotics: because phages infect and kill bacteria using different mechanisms to those of antibiotics. Consequently, phages can be effectively used to treat antibiotic-resistant infections such as those caused by multidrug-resistant Staphylococcus aureus (Loc Carrillo and Abedon, 2011).

5. Nontoxic effects: some toxicity studies performed with phages in experimental animals such as chickens and mice have shown no toxic effects or adverse reactions in animals (Xie et al., 2005; Gill et al., 2006). Furthermore, they are recognized to be harmless to humans and animals, since recently their use has been approved as an additive in human foods and for direct application in animals (Carlton et al., 2005).

6. Possible phage transfer between individuals: this is essentially a cross-infection of phages from treated subjects or environments to untreated individuals, which may be potentially useful in agricultural applications (Rozema et al., 2009).

7. Low environmental impact: because of their chemical composition and their narrow host range, phage eliminated after treatment, unlike broad-spectrum antibiotics, in the worst scenario will impact only a small group of environmental bacteria (Loc-Carrillo and Abedon, 2011).

8. Low cost: the production of phages predominantly involves growth in its host and further purification. Overall production costs of phages, per unit, do not compare to the costs of pharmaceutical production, while the cost of discovery, isolation, and characterization can be relatively low (Loc-Carrillo and Abedon, 2011).

2.4.2. Potential drawback of bacteriophage therapy

Otherwise, the disadvantages of using phages as therapeutic agents the following are described:

1. Existence of phage-resistant bacteria: bacteria can evolve resistance to bacteriophages through a variety of mechanisms, including the blocking of viral adsorption, inhibition of the viral genome injection, restriction-modification systems mediated by enzymes that degrade viral nucleic acids or the CRISPR-Cas system (Bikard and Marraffini, 2011), and infection abortion systems of resistance conferred by the Abi system (Buckling and Brockhurst, 2012).

2. Not all phages are good therapeutic agents: good therapeutic phages must have a high potential to reach and then kill the bacteria, along with a low potential to modify adversely the environments in which they are applied (Loc-Carrillo and Abedon, 2011).

3. Narrow host range: the narrow host range of phages could constitute, at least, a limitation for presumptive treatment. However, as phages may be used in combination with other antimicrobial agents, including other phages, the lytic spectrum of these particles can be much broader than the spectrum of activity of a single phage (Loc-Carrillo and Abedon, 2011).

4. Need for high bacterial concentration: this is a needed requirement for the phage to replicate and lyse bacteria. If they are administered in a hurry they will tend to inactivate due to lack of bacteria and higher concentrations will be needed later (Payne and Jansen 2001).

5. Interaction of bacteriophages with the innate immune system: may lead to low efficiency of phage therapy (Dombrowsk et al., 2005).

6. Existence of physical and chemical barriers that may reduce the phage-bacterium interaction: an example of this has been observed in orally administered phage therapies, where the gastrointestinal environment determines a decrease in the effective encounter between the bacteriophage and the challenge strain (Sklar and Joerger, 2001) since the virus can experience structural problems due to action of digestive enzymes and pH conditions found in the gastrointestinal tract (Higgins et al., 2007).

7. Limited knowledge about the pharmacology of phage: this proves to be another big issue (Dabrowska et al., 2005)

8. Consumer perception problems: This situation would be resolved by educating consumers about the safety of the use of phages, and also through the use of new molecules derived from phages, such as endolysins or purified lysozyme (Borysowski and Weber-Dabrowska, 2008).

2.5. Efforts Made in Ethiopia Regarding Bacteriophages Therapy

Generally, there is limited study on phage isolation and their therapeutic potential, particularly, against multi-drug resistant pathogen in Ethiopia. However, bacteriophage having ability of lysing MDR Escherichia coli was isolated and demonstrated by Getachew and his co-worker. Moreover, very few review articles on phages, which are done by some universities from Ethiopia, were existed in scientific journals. Efforts made in Ethiopia are specifically paying attention on isolation of bacteriophages from natural sources (Nureye et al., 2018)

3. CONCLUSION AND RECOMMENDATION

In an era of increasing emergence of multi-drug resistant pathogens and a scarcity of new antimicrobials, there is an urgent need to find antimicrobial alternatives. Phage-based solutions presented here in have potential as therapeutic or prophylactic tools for application in human animal. Bacteriophages have several characteristics that make them potentially attractive therapeutic agents. They are highly specific and very effective in lysing targeted pathogenic bacteria, safe and rapidly modifiable to combat the emergence of newly arising bacterial threats. In addition a large number of publications, some of which are reviewed in this review, suggest that phages may be effective therapeutic agents in selected bacterial infection of animal. Bacteriophage therapy may be in future effective therapeutic tool for management of bacterial infection. Well-organized research and more evidence from high-quality clinical trials will be needed to increase confidence in the breadth of their effectiveness.

Depending on the above fact the following points are recommended:

- Well organized research and substantial academic efforts should be made to realize complete phage therapy utilization in veterinary medicine
- Facilitating and organizing workshops as well as training to provide information concerning the possible use of bacteriophages should be made
- Clear legal regulations must be established to define limitations and the safe use of phage therapy
- Lastly, bacteriophage therapy should be enhanced and application should be adopted in developing countries like Ethiopia

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