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REVIEW

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Bacteriophages: an overview of the control strategies against multiple bacterial infections in different fields

Muhsin Jamal[1] | **Sayed M. A. U. S. Bukhari**[1] | **Saadia Andleeb**[2] | **Muhammad Ali**[3] | **Sana Raza**[4] | **Muhammad A. Nawaz**[5] | **Tahir Hussain**[1] | **Sadeeq u. Rahman**[6] | **Syed S. A. Shah**[7]

[1] Department of Microbiology, Abdul Wali Khan University, Garden Campus, Mardan, Pakistan

[2] Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan

[3] Department of Life Sciences, School of Science, University of Management and Technology (UMT), Lahore, Pakistan

[4] Institute of Health Sciences, Mardan, Pakistan

[5] Department of Biotechnology, Shaheed Benazir Bhutto University, Sheringal, Dir (Upper), Pakistan

[6] College of Veterinary Sciences and Animal Husbandry, Abdul Wali Khan University, Garden Campus, Mardan, Pakistan

[7] Department of Zoology, Abdul Wali Khan University, Garden Campus, Mardan, Pakistan

Correspondence
Muhsin Jamal, Department of Microbiology, Abdul Wali Khan University, Garden Campus, Mardan, 23200, Pakistan.
Email: muhsinkhan08@gmail.com

Bacteriophages (phages/viruses) need host bacteria to replicate and propagate. Primarily, a bacteriophage contains a head/capsid to encapsidate the genetic material. Some phages contain tails. Phages encode endolysins to hydrolyze bacterial cell wall. The two main classes of phages are lytic or virulent and lysogenic or temperate. In comparison with antibiotics, to deal with bacterial infections, phage therapy is thought to be more effective. In 1921, the use of phages against bacterial infections was first demonstrated. Later on, in humans, phage therapy was used to treat skin infections caused by *Pseudomonas* species. Furthermore, phages were successfully employed against infections in animals – calves, lambs, and pigs infected with *Escherichia coli*. In agriculture, for instance, phages have successfully been used e.g., Apple blossom infection, caused by *Erwinia amylovora*, was effectively catered with the use of bacteriophages. Bacteriophages were also used to control *E. coli*, *Salmonella*, *Listeria*, and *Campylobacter* contamination in food. Comparatively, phage display is a recently discovered technology, whereby, bacteriophages play a significant role. This review is an effort to collect almost recent and relevant information regarding applications and complications associated with the use of bacteriophages.

KEYWORDS
bacteriophage, endolysins, lysogenic, lytic, phage therapy

1 | INTRODUCTION

Bacteriophages or phages are small viruses ranging in size from 20 to 200 nm. They are dependent exclusively on biosynthetic machinery bacteria for their replication and propagation [1]. Phages play important role in the ecosystem [2] and were independently discovered by two scientists – Fredrick Twort (in 1915) and Felix d'Herelle (in 1917). Temperature, available nutrients, light and other environmental factors influence generation of new phages [3]. Coat protein encapsidate the genetic material (be either DNA or RNA) of the phage [4].

Lytic or virulent and lysogenic or temperate are the two types of infection over which phages can be classified [5]. In lytic cycle, the degradation of host DNA occurs and different proteins are formed including capsid protein, lysis protein,

etc. New phages are produced inside the bacterial cell. Phages use the synthetic machinery of the host, and approximately 50–200 phages are produced which exert pressure on bacterial cell wall to rupture the cell and the phages are subsequently released. This interaction is termed as master-slave relationship [6]. In case of lysogenic life cycle, the phage DNA is incorporated in host DNA, phage DNA is replicated with host DNA and thus remain cryptic entities. The integrated phage DNA is termed as prophage. Lytic genes are also present in temperate bacteriophages but did not express due to unknown reasons. This kind of interaction is called host–guest relationship [7]. Ultimately during their life cycle, the virulent genes are expressed and the lysogenic life cycle is converted into lytic cycle.

Although a single antibiotic is used to treat different bacterial infections, a number of bacteria are now resistant to multiple antibiotics – including *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and MRSA [8,9]. Antibiotics, therefore, may not be considered as a potential and viable option for bacterial control and management. Phages, the most common virus in the biosphere, can easily be found and isolated from all those environments where bacteria can exist [10–12]. Recently, with the advent of biotechnology, bacteriophages have been used to treat bacterial infections. Phages are commonly used as antibacterial agents and in phage display systems [4]. They can also be used for the treatment of most lethal and life threatening bacterial diseases and complications in humans, animals, and plants [13,14]. Some of the FDA-approved phage-based products are given in Table 1. Other applications include, but not limited to, the control of food contaminants [12,15]. This study is an effort to collect and analyze relevant information encompassing the phage potential and application.

2 | HISTORICAL BACKGROUND

Ernest Hanbury Hankin in 1896 discovered bacteriophages in Indian rivers, namely Ganges and Yamuna. These bacteriophages displayed surprising features like antibacterial properties against cholera and could filter through very fine porcelain [16]. Later on, in 1917, Fleix d'Herelle (1873–1949), a self-taught French-Canadian bacteriologist, coined the name Bacteriophage (from the Greek *Phagein* meaning to eat) for the first time [17]. He noted a man suffering from dysentery and utilized bacteriophage to restore health [18,19]. In France since 1919, the phage therapy is in practice [20]. Several trials were reported from Baylor University College of Medicine in 1923. To sum up, phages are weapon for fighting against different bacterial infections [21,22].

3 | MORPHOLOGY

Bacteriophages consist of capsid (head) and/or tail with some exceptions [23]. The capsid encapsidates and protects genetic material, DNA or RNA [24]. Bacteriophages vary in size ranging from 24 to 400 nm [25]. The capsid has usually geometric shape with two or more different proteins. Some bacteriophages are filamentous while others are icosahedral (20 facets). The capsid is important because it inhibits enzymes from exploiting the genetic material [26]. Tails are attached to the phage capsid through a connector (Fig. 1). Along with other roles of bacterial strain recognition, connector helps transfer the genetic material into the host cell [27]. When a phage is lingered to the host, specific signals are transmitted from the tail to capsid. The connector is, hexagonal, hetero-oligomer composed of several proteins that lyse bacterial cell wall and paves

TABLE 1 List of FDA-approved phage-based products

Product and company	Regulatory approval	Applications	Ref.
ListShield, Intralytix, Inc. USA	US FDA (2006) and USDA for direct application onto foods (21 CFR 172.785.) EPA (EPA registration 74234-1)	Ready to eat food: salami, sausage, basterami, sea food, food contact surfaces and environments	[130]
EcoShield, Intralytix, Inc. USA	FDA (2011) cleared as "Food Contact Notification" or FCN, (FCN No. 1018). FSIS Directive 7120.1 (safe and suitable antimicrobial)	Red meat parts and trim intended to be ground	[131]
SalmoFresh, Intralytix, Inc. USA	FDA (GRAS Notice No. GRN 000435), FSIS Directive the Star K-certified Kosher and IFANCA-certified Halal product. OMRI-listed suitable in the production of organic foods	Poultry, fish and shellfish, fresh and processed fruits and vegetables	[132]
LISTEX Micreos EBI, Food Safety, Netherlands	In 2006 approved by the FDA as GRAS, and by the USDA in 2007 and by the EFSA, Health Canada, BAG (Switzerland) and FSANZ (Food Standards Australia New Zealand)	Ready to eat meat, fish, cheese	[133]
Agriphage, Omnilytics USA	EPA 2005 for use in agriculture	In agriculture on fruits and vegetables	[134]

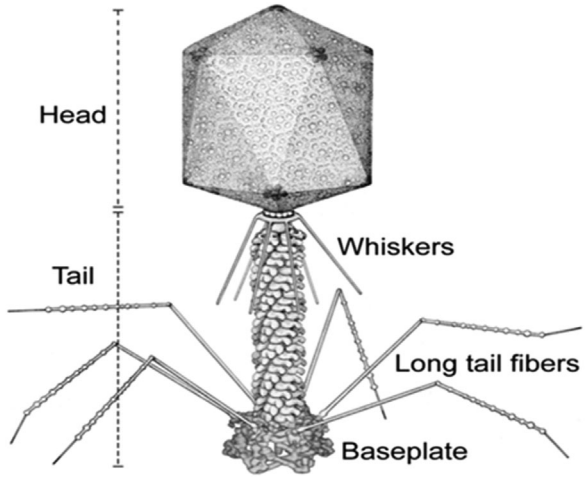

FIGURE 1 Structure of a typical bacteriophage. A typical bacteriophage is like a tadpole shaped consists of a head, enclosing the nucleic acid, a base plate and a tail having tail fiber. The structure has been adapted from Yap et al. [128]

way to transfer genetic material from the capsid to the host bacterium [28,29].

4 | NATURE

Phages are intracellular obligate parasites that replicate utilizing bacterial machinery. Without the host (bacteria) they could not replicate [1] in nature. Phages are probably the most ancient and ubiquitous existing organisms on the earth and could be found in very large number [2]. Phages are found in very diverse environments, i.e., in feces, soil, water, etc. By exploiting host machinery, they synthesize different cellular components, like proteins and glycoproteins required for their replication, encapsidation, lysis, etc. [30].

5 | CLASSIFICATION

Electron microscopy has been extensively used to characterize approximately 5000 phages [31]. Phages are classified into two groups – virulent and temperate phage. The example of virulent phages like T4 virulent phages undergo lytic life cycle [32]. The genetic material of phage is transferred to the cytoplasm of the bacterial cell while capsid and tail remain outside of the cell [33]. Synthesis of different components occurs, such as structural and non-structural phage proteins. After biosynthesis of different components, viral assembly takes place. Release of progeny into the exterior in case of most phages can only be done once the host cell is burst open [30]. In lysogenic life cycle, the viral DNA is integrated into bacterial chromosomal DNA, known to be a prophage. Lytic genes are also present in temperate bacteriophages but they are not usually expressed may be due to the presence of repressors. Later in infection the switching of lysogen, bacteria with integrated genomes, to the lytic form occurs [34]. Phage nucleic acid may either be single or double stranded [35]. Most of the phages consist of dsDNA genomes. Some other kinds are known that include ssRNA genomes, dsRNA genomes, and ssDNA genomes [30].

6 | LIFE CYCLE

Bacteriophages have two life cycles one is lytic or virulent, while the other is lysogenic or temperate life cycle [36].

6.1 | Lytic cycle

Immediately after the integration of genetic material, the phage life cycle is said to be eclipse period [37]. The eclipse period is the time between infections caused by a bacteriophage or any other virus, and the appearance of mature virus within the host cell [38]. Ultimately, the genetic over the control of host biosynthetic machinery. Different proteins are formed separately inside the bacterial cell, they include synthesis of coat protein, which helps in the formation of capsid, and proteins like lysis proteins that cause lysis of the host cell [30]. The genetic material is packed inside the capsid and the tail is added to the head. Phage components are assembled into mature virions. Lysis of bacterial cells occur due to the accumulation of phage lysis proteins. The bacterial cell ruptures and new phages are released into the medium (Fig. 2), which are then ready to start another infection cycle [36].

6.2 | Lysogenic cycle

The phage DNA is replicated along with bacterial DNA, thereby establishing a stable relationship [39]. Generally in this cycle the viral DNA is integrated into the host bacterial chromosomal DNA (Fig. 2). In later stages during this life cycle the switching of lysogen to the lytic form occur leading to the activation of lytic life cycle [30,34,39].

7 | APPLICATIONS OF BACTERIOPHAGES

7.1 | Phage therapy

Herelle named viruses that kill bacteria as bacteriophages. He was the first person who directed much research on bacteriophage and presented the idea of phage therapy [19]. Phages had widespread use, including treatment of bacteria like *Staphylococcus*, *Pseudomonas*, *Proteus* spp. In the west, and specifically the US, phages were used extensively.

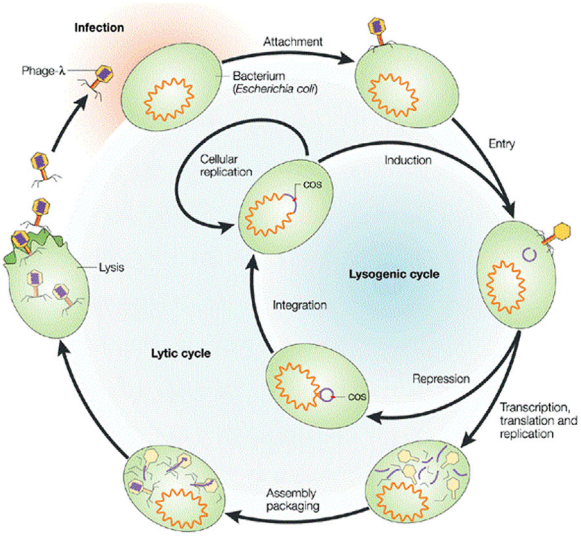

FIGURE 2 Lytic and lysogenic cycles of lambda (λ) bacteriophage reproduction. Two types of life cycle of lambda (λ) phages exist, lytic and lysogenic cycle. In the lytic case the phage attached to the host cell and injects its nucleic acid. Afterwards transcription, translation and replication occur followed by phage assembly. Finally the host cell is rupture due to pressure exerted by phage progeny. On the other hand, in the lysogenic life cycle, the phage nucleic acid after getting entrance is integrated into bacterial chromosome. The prophage, integrated phage DNA, can revert to virulent form if it is excised from the bacterial genome, usually in response to certain environmental stimuli such as radiations or the presence of some chemicals, and starts the lytic cycle. Figure adapted from Campbell [129]

However, with the advent of antibiotics phage therapy has declined in its application. Phage therapy research used to continue in Eastern Europe [40]. Development of antibiotic resistance in bacteria necessitates the importance of phage therapy. It is widely presumed that phage therapy is more effective than antibiotics. Comparison of phage and antibiotics is shown in Table 2 [41]. There are many applications of phage therapy including, but not limited to, agriculture, veterinary, oceanology and medical sciences. Scientists are paying much attention to animals' models utilizing phages for modeling human infections [42].

7.2 | Phage expression system

Phages are too much effective against various bacterial infections. One of the reasons is that phages produce proteins, endolysins that help degrade the peptidoglycan layer in bacterial cell wall [43]. Endolysins are also used initially for host penetration. These enzymes released by bacteriophage affect the cell wall and break up the bonds between the peptidoglycan components [44]. The enzymes that naturally occur in phages are effective against any kind of bacteria. They make pores in bacterial cell wall and destroy all bonds among the peptidoglycan. These enzymes kill a vast range of bacteria [45]. This property of bacteriophages may better be utilized against several bacterial infections in humans, animals, plants, and marine organisms [13].

7.3 | Bacteriophage therapy for humans

Taking as an opportunity, phages can be utilized for different bacterial infections [46]. Phages were used in 1919 for human bacterial infections [47]. Some bacteria are beneficial for human such as body's normal flora, while other bacteria cause infections in the human body [48]. The main reservoir of these bacteria are in the respiratory tract – upper and lower, intestinal urogenital tracts, etc. Some of the bacteria are resistant to certain antibiotics. The pathogenic bacteria like, Pneumococci, Staphylococci, and Streptococci are present in the environment are also found in the human body in different areas [49]. Some bacteria use the way of nose for the entrance in the human body. Phage lytic enzymes can be better used for the decrease of nasopharyngeal (nose and pharynx) carriage of pathogens [50]. Phages are used in newborns for the treatment of meningitis of brain and spinal cord. The fatal infection can successfully be treated with phages [51]. Several bacteria have been identified causing skin infections, e.g., *Pseudomonas* species. Similarly, lung infections are caused by *Staphylococcus*. Whereas, *P. aeruginosa* causes cystic fibrosis. These very diverse bacterial infections were successfully treated with phages [52,53]. Phages are used for clinical enhancement related to the quickly removal of *S. aureus* that are multidrug – methicillin, penicillin, and ciprofloxacin – resistant bacteria [54]. For the most lethal infections like methicillin-resistant *Staphylococcus aureus* (MRSA), oral therapy could be used to treat the disease or infections [55]. Phage lysin enzymes are used for the treatment of anthrax, caused by *Bacillus anthracis* [56]. In the treatment of anthrax, lysin played a very critical role by injecting phage lysin intravenously to manage the entrance of the bacteria [57]. Collectively, in Eastern Europe researchers work on the phage therapy to control bacterial infections in humans to cater life threatening diseases [58].

7.4 | Veterinary sciences

Phages can be used in veterinary medicine to deal with bacterial infections [59]. One of the most lethal bacterial infections is murine salmonellosis. Mice were used as animal models for phage therapy by infecting it with several serotypes of *Salmonella* and significant effects were observed in reducing or inhibiting these infections [47]. Bacteriophages have been successfully used against bacterial infections in livestock and other animals. Two scientists, namely, Smith and Huggins worked on bacteriophage against animal diseases. Smith and Huggins used bacteriophage therapy in

TABLE 2 Comparison of phages and antibiotics

S no.	Bacteriophages	Antibiotics	Ref.
1	Very specific (i.e., usually affect only the targeted bacterial species); therefore, dysbiosis and chances of developing secondary infections are avoided	Antibiotics target both pathogenic microorganisms and normal microflora. This affects the microbial balance in the patient, which may lead to serious secondary infections	[135]
2	Replicate at the site of infection and are thus available where they are most needed	They are metabolized and eliminated from the body and do not necessarily concentrate at the site of infection	[136]
3	No serious side effects have been described	Multiple side effects, including intestinal disorders, allergies, and secondary infections (e.g., yeast infections) have been reported	[137]
4	Phage-resistant bacteria remain susceptible to other phages having a similar target range	Resistance to antibiotics is not limited to targeted bacteria	[138]
5	Selecting new phages (e.g., against phage-resistant bacteria) is a relatively rapid process that can frequently be accomplished in days or weeks	Developing a new antibiotic (e.g., against antibiotic-resistant bacteria) is a time-consuming process and may take several years	[139]

animals; such as to treat calves, lambs and pigs infected with *Escherichia coli* [60]. Phages are also successfully used against skin infections caused by *P. aeruginosa*. In mice, *P. aeruginosa* infections have been successfully controlled by using phages [61].

In later studies, bacteriophages were used against mice and pigs bacterial diseases caused by *P. aeruginosa* and *Acinetobacter baumanii*. Phages were able to stop the skin grafts caused by *P. aeruginosa* infections [60–62]. *Staphylococcus aureus* that infects mice was successfully treated by phages [63]. Phages encode lysin enzyme and when a small amount of lysin is added to the infectious area, all of the bacteria are destroyed within 2–5 h [64]. Bacteriophages are used against environmental sanitation that is to clean up the environment from different bacteria, in general from different pathogens. Phages have been used successfully to treat sewerage water against several pathogenic bacteria such as *S. aureus*, *E. coli*, and others [65].

7.5 | Agriculture

Phages are used worldwide in agriculture preferably for bacteria resistant to antibiotics [66]. The antibiotic resistant bacteria causing bacterial blight on soybeans was successfully treated with phages [67]. Recently, food and drug administration (FDA) has approved certain phages for use on crops to reduce the disease load. Continuous efforts are there to identify and isolate potential phages to treat diverse bacterial diseases on crop plants [68].

Modern studies show the effectiveness of phage therapy in crops. Banana is infected with a bacterium called *Ralstonia solanacarum*, phages are used against this pathogen to reduce or to destroy its pathogenicity. In one of the experiments, phages were successfully used against different pathogenic strains of *R. solanacarum* [69]. Bacterial blight, drying of leaves, and ultimate death of the infected plants is found in soybean that is caused by *P. syringae* pv. *glycinea*. A cocktail of three phages were used that protected the plant successfully [67].

Similarly, the drastic disease of apple – blossom infection – caused by the pathogen called *Erwinia amylovora* was effectively controlled by the use of bacteriophages [70]. Other infections caused by *R. solanacearum* and *Xanthomonas campestris* causing bacterial wilt and blot, respectively, in variety of different plants were also efficiently controlled by using bacteriophages [71]. Besides applications of bacteriophages, phage producing endolysin gene was expressed in tomato [72]. The transgenic tomato plant when infected with pathogen *Clavibacter michiganensis*, lesser symptoms of infection were observed showing that endolysins has provided protection against the bacteria [73].

7.6 | Food safety

People consume food but it is not always free from pathogens. Food usually contains different pathogens that may cause serious diseases in humans [74]. Four different pathogens that contaminate the food are *Salmonella*, *Campylobacter*, *E. coli*, and *Listeria*. These bacteria cause lethal infections in human, and also may generate many complications [75].

7.6.1 | Control of *E. coli* O157:H7 contamination

E. coli, gram-negative bacteria, is known as one of the most drastic bacteria. The main reservoir of *E. coli* is human intestine and can be easily isolated from feces. This bacteria cause a number of lethal diseases in humans as well as in animals, in humans it cause acute diarrhea, for instance [76]. The bacterium *E. coli* is known to cause contamination in animal products. The phage CEVI successfully reduced the pathogenic strain of *E. coli* achieved within 2 days of oral

administration in sheep [77]. The most pathogenic strain, *E. coli* O157:H7 that causes severe diarrhea in human if its load is increased i.e., more than 100 cells [78]. Phages were used against cattle infections; orally administered phage KHI was not effective. So the combination of phages was used, i.e., KHI and SHI phages were observed to reduced number of bacterial cell [79]. Furthermore, phage cocktails were successfully used to prevent/control pathogen contamination from the meat surface [80].

7.6.2 | Control of *Salmonella* contamination

Salmonella causes many serious infections in humans, i.e., food-borne illnesses [81]. Different infections of *Salmonella* are successfully reduced by bacteriophages. *Salmonella* causes contamination in cheeder cheese but in the presence of a phage, with multiplicity of infection (MOI) 104, *Salmonella* did not survive in pasteurized cheese after 89 days, but was available in raw milk cheese [82]. Additional studies on the *Salmonella* phage felix-O1 were performed using it as biocontrol agent on the *S. typhimurium* on chicken's frankfurters [83].

7.6.3 | Control of *Listeria monocytogenes* contamination

L. monocytogenes causes a number of food-borne diseases called listeriosis. This bacterium has the ability to replicate at refrigeration temperatures making it one of the most important pathogen [84,85]. *Listeria* causes a number of infections in fresh fruits such as apple and melon. Using phages in the combination with bacteriocin (nisin), the number of pathogens decreased in apple and other fresh fruits [86]. *Listeria* is found in everywhere in the environment. Therefore, the phage treatment mainly occurs in the final process in the industries during packaging that help to secure the food for long time [84,87].

7.6.4 | Treatment of *Campylobacter*

Campylobacter is also associated with food-borne diseases and illnesses, specifically, the pathogenic strains like *Campylobacter jejuni* and *Campylobacter coli* [88]. The optimum growth of the bacteria is at 41 °C. Approx. 400–500 cells of *Campylobacter* can cause infection in human body [89]. For all these infections, bacteriophages were applied to reduce the pathogenicity of particular pathogen and recover good health [90].

7.7 | Phage display technology

Phage display is a laboratory technique for the study of protein–protein, protein–peptide, and protein–DNA interactions that uses bacteriophages to connect proteins with the genetic information that encodes them [91]. In this technique, a gene encoding a protein of interest is inserted into a phage coat protein gene, causing the phage to "display" the protein on its outside while containing the gene for the protein on its inside, resulting in a connection between genotype and phenotype [92]. These displaying phages can then be screened against other proteins, peptides or DNA sequences, in order to detect interaction between the displayed protein and those other molecules [93].

Phage display was first described by George P. Smith in 1985, when he demonstrated the display of peptides on filamentous phage by fusing the peptide of interest onto gene III of filamentous phage [93]. The most common bacteriophages used in phage display are M13 and fd filamentous phage [94,95]. The phages T4 [96], T7 and λ have also been used for phage display.

Phage display technology offers potential tools for development of therapeutic agents, vaccines, diagnostic reagents, as well as gene and drug delivery systems [97]. Determination of interaction partners of organic (proteins, polysaccharides or DNAs) or inorganic compounds and also *in vitro* protein engineering are the major applications of phage display technology [98]. More recently, a number of attempts have been made for using *in vitro* phage display technology in medical science by designing humanized antibodies or peptides and development of new pharmaceutics for various maladies such as cancer, autoimmune and inflammatory diseases, metabolic and allergic disorders [99]. This methodology has usually been applied for the production and isolation of the antibodies [100]. The technique is also used to determine tumor antigens for use in diagnosis and therapeutic targeting [101] and in searching for protein–DNA interactions using specially constructed DNA libraries with randomized segments [102]. At present, >20 phage display-derived antibody and peptides are in late-stage of clinical trials or have been approved [103–107].

7.8 | Antibody derivation

The first monoclonal antibodies (mAbs) were produced by using the hybridoma technique in 1975 [108]. Over the past 40 years, a great number of mAbs have been prepared and characterized against various antigens. Nevertheless, only a few of these antibodies have presented clear clinical benefit in treatment of diseases [106–109]. These antibodies are widely used for development of diagnostic tests [110–112] such as enzyme immunoassays [113,114], immunochromatography [110,115,116], and immunosensors [117,118].

The most successful phage display-derived antibodies that underwent clinical or preclinical trials are summarized in later studies [100,103–105,107,119,120]. Firstly, Adalimumab is a recombinant human IgG1 mAb that is used as a

TNF-inhibiting anti-inflammatory drug. It washed first fully human mAb drug approved by the FDA for treatment of seven symptoms: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis [105,121,122]. Secondly, Belimumab is a humanized antibody that inhibits B-cell activating factor. It was generated by phage display for the treatment of autoimmune diseases, mainly systemic lupus erythematosus, approved in the US, Canada, and Europe [123]. Thirdly, Raxibacumab is a human mAb intended for the prophylaxis and treatment of inhaled anthrax. This antibody binds to the protective antigen (PA83) of *Bacillus anthracis*. Its efficacy has been proven in rabbits and monkeys [124]. In December 2012, Raxibacumab was approved for the treatment of inhalational anthrax raised from *B. anthracis* in combination with appropriate antibacterial drugs. It can also be used for prophylaxis of inhalational anthrax when alternative therapies are not available or inappropriate [107]. Fourthly, in the recent years, considerable numbers of peptide drugs have been approved or are under clinical studies for a wide variety of diseases such as AIDS and other malignancies. Several selected successful therapeutic peptides isolated from phage display, which have been approved or are under clinical studies, are listed along with their functions, indications, and manufacturers [125–127].

8 | CONCLUSIONS

Applications of bacteriophages range from the diagnosis of bacterial diseases, through phage typing, to disease prevention (phage vaccine) and control/treatment (phage therapy). Phages could be useful in ways never explored before – specifically, cocktail/combination of phages would be easy to treat a wide variety of bacterial infections that are considered resistant to even the latest generations of antibiotics. Besides utilizing the lytic potential of phages, their versatility also allows using antibodies. Similarly a protective antigen could be delivered as a DNA or phage display vaccine. Also, a mixture of genetically modified phages would be more helpful. Phage derived endolysin has much potential to be explored extensively for its utilization against gram positive bacteria. However, there is a need to investigate widely the interaction of bacteriocins in the context with phage application. Phages also are known to cater food spoilage problems and bacterial infection of plants and fruits. The concerns regarding utilization of phages as antibacterial agents include mainly, safety and efficacy issues and development of a potential immune response towards any administered phage. Growth optimization and purification strategies of phages are also some issues needed to be addressed. Advances in biotechnology and molecular biology could address complexities that human are facing today.

CONFLICT OF INTEREST

The authors declare that no financial or any other conflicts of interest associated with the present manuscript exist.

ORCID

Muhsin Jamal http://orcid.org/0000-0003-4415-2412

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