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Review Article

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Bacteriophage Therapy-A Novel Approach against Bacterial Biofilm Related Infections

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Abstract

According to WHO (World Health Organization), the existence of bacterial biofilm is a serious health threat to healthy civilization. Bacterial biofilm are the predominant cause of chronic infections and several diseases due to its multi-drug resistant nature. So it is difficult to treat the biofilm with conventional antimicrobial compounds as most of the biofilms are resistant to them. Therefore, it is very important to find out new novel strategies which can efficiently fight against bacterial biofilm. Bacteriophages are the viruses that only attack bacterial cells but not humans. So, it could be a novel strategy to eradicate bacterial biofilm related infections. As bacteriophage has no side effects on human, they are considered as safe alternatives to antimicrobial compounds. Bacteriophages have great potential in medical industries, food industries, and pollution control. There are several types of phage therapy to control biofilm, including combinatorial phage therapy, in which bacteriophages are applied to treat bacterial biofilm in combination with other antimicrobial compounds and other bacteriophages. The combination of variety of bacteriophages are known as phage cocktail. In this present study, we discuss about the phage therapy and its application as a novel technique to eradicate or inhibit pathogenic bacterial biofilm to maintain healthy human health and a healthy environment.

Keywords: Bacteriophage, Bacterial Biofilm, Phage Therapy, Multi-drug Resistant Bacteria, Phage Cocktail, Phage encoded enzymes.

1. Introduction

The biofilm formation by bacteria increases their survivability and virulence that making them more potent pathogenic to cause many chronic human infections, which are very difficult to treat. Infections with these pathogens lead to diseases with a high mortality rate. Excessive uses of broad-spectrum antibiotics are the major cause of the emergence of antibiotic-resistant bacteria and the increase of multi-drug resistance in bacterial strains become a major public health problem, especially in the hospital, that leads to hospital-acquired or nosocomial infection (Broncano-Lavado *et al.*, 2021).

Bacteriophages are viruses that specifically infect and multiply inside the bacterial cell. Though in 1917, Felix d'Herelle first coined the term bacteriophages, however, in 1915, British bacteriologist Frederick Twort first experimentally showed the existence of some microorganisms antagonistically on specific bacterial cells (Sadekuzzaman *et al.*, 2018). According to their life cycle, they are classified as lytic and lysogenic phages. lytic phages can lyse the bacterial cell wall using the endolysin enzyme and help to eradicate biofilm (Clokie *et al.*, 2011). According to preclinical studies phages have unique capabilities for targeting bacterial infections by breaking down biofilms. Genetically modification in bacteriophages also enhances their antimicrobial and antibiofilm effect (Akanda, Taha and Abdelbary, 2018). Phage therapy is an alternative way to antibiotics for their valid characteristics such as having antimicrobial and antibiofilm activity and environmental safety (Tian *et al.*, 2021).

A single bacteriophage or bacteriophage cocktail (two or more bacteriophages) can be used for phage therapy, but bacteriophage cocktail is more effective against bacterial infections as its higher reduction of bacterial density. *In-vivo* as well as *in vitro* studies suggests that bacteriophage cocktail improves bacteriophages' efficiency. Bacteriophage preparation can easily penetrate the extracellular polymeric substances (EPS) matrix of biofilm and disrupt its complex structure by polysaccharide depolymerase or hydrolase enzyme synthesis. Studies revealed that bacteriophages can inhibit quorum sensing activity required for biofilm formation by synthesis of quorum quenching (QQ) lactonase (Chegini *et al.*, 2020).

Therefore, it is very important to understand the structure and formation process of biofilm to find out new promising strategies to combat with biofilm related chronic infection and emerging antibiotic resistance. In this review, we will comprehensively summarize and discuss the importance of bacteriophages and bacteriophage derived compounds in the inhibition and eradication of microbial biofilm formation and the application of phage therapy as a possible effective strategy against multi-drug resistant (MDR) bacterial infections for clinical purposes.

2. Structural Characterization and Formation of Biofilm

A bacterial biofilm is a complex and potent community of self-adhered or surface-colonized cells, enclosed in a self-secreted matrix of extracellular polymeric substances (EPSs), that are composed of polysaccharides, proteins, lipids, and a small number of nucleic acids (Łusiak-Szelachowska, Weber-Dąbrowska and Górski, 2020). EPSs are essential for the structural stability of the microbial cells in the biofilms (Topka-Bielecka *et al.*, 2021). Attachment of planktonic cells to the surface through their pili, fimbriae, and flagella; is the first stage of biofilm formation. Many forces including electrostatic interaction and van der Waals forces are responsible for this attachment. Then the bacterial cells form a monolayer consisting of a self-secreted EPS matrix in the surrounding environment that helps to develop a mature biofilm. At last, bacterial cells start to multiply quickly within the biofilm and start to detach followed by dispersing as planktonic forms, that colonize again on new surfaces. Extracellular DNA (eDNA) is one of the major structural component of biofilms, that play important role in biofilm formation and protects the bacteria from antibiotics and the host immune system (Shrabasti Bandyopadhyay, Samik Biswas, 2021). EPS acts as a protective barrier against antibiotics that are responsible for the development of drug resistance. EPS also acts as a source of nutrients, which facilitate bacterial growth (Łusiak-Szelachowska, Weber-Dąbrowska and Górski, 2020).

3. Bacterial Biofilm Related Infections

Bacterial biofilms are responsible for many chronic infections in humans, as biofilms show resistance to the host immune system and many antibiotics due to their complex structure, which makes them multi-drug resistant (MDR). Biofilms

can easily form on medical devices such as catheters, orthopedic implants, pacemakers, prostheses, contact lenses, and even in host tissue, wounds, and mouth cavity and cause serious health problems. Biofilm related infections are sometimes chronic such as urinary tract infections, orthopedic-implants related diseases, endocarditis, sinusitis, otitis, cystic fibrosis, wound infection, periodontitis, and dental caries (Sharma, Misba and Khan, 2019). Biofilms may contain either a single or a mixture of different types of bacteria. In the environment, there are wide varieties of biofilm forming microorganisms that cause life threatening infections (Table-1). Even microbial biofilms are major problems in the food industry also. Microorganisms such as *Salmonella spp., E. coli, Shigella spp., S. aureus, Vibrio spp., Campylobacter jejuni, Clostridium spp.*, and *Listeria monocytogenes* are the major biofilm forming bacteria in the food industry (Sadekuzzaman *et al.*, 2018).

Table-1: Causative pathogens for biofilm related diseases (Topka-Bielecka *et al.*, 2021)

Surfaces for biofilm formation	Pathogens
Venous Catheters	*Pseudomonas aeruginosa*, *Enterobacter spp.*, and *Klebsiella spp.*
Urinary Catheters	*Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *P. aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and other Gram-negative Bacteria
Contact Lenses	*E. coli*, *P. aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*, *Serratia* spp., and *Proteus spp*. bacteria and various species of the *Candida* genus
Dental Plaque (Dental Caries)	*Pseudomonas aerobicus* and *Fusobacterium nucleatum*. They are the main agents of gingivitis and periodontitis
Lung Infection (Cystic fibrosis)	*P. aeruginosa*

4. Biofilm combating strategies using bacteriophages

Bacteriophages, also known as phages are naturally occurring viruses that only infect bacterial cells. The biological system possesses a diverse variety of host bacteria specific bacteriophages. The bacteriophage infection occurs in several stages, such as attachment to the bacterial cells, injecting phage genomic components into the bacterial cell's cytoplasm, production of viral virions and assembly of phage components, lysis of the host bacterial cells, and release of mature phage (Resistance, 2021). They are subdivided into two categories, such as virulent or temperate, depending on the lytic and lysogenic cycle (*Frederick William Twort: not just bacteriophage | Microbiology Society*, no date; Sadekuzzaman *et al.*, 2018; Gordillo Altamirano and Barr, 2019; Broncano-Lavado *et al.*, 2021).

These two are the reproductive cycles of bacteriophages where on one hand, in the lytic cycle phages attack the bacterial cells and after attaching to the bacteria they release the viral genomic component into the bacterial cells. After entering into the bacterial cells, phage DNA and several restriction endonucleases chopped the bacterial genome and produce virions or viral components. Then those viral components are assembled within the bacterial cells and release the mature phage viruses from the host bacteria by lysis of the cells. On the other hand, in lysogenic cycle, after entering into the bacterial cells, phage DNA inserts into the bacterial genome and stayed in a dormant stage, which is

an inactive condition. In this stage viral genome, replicates with the bacterial genome till the environmental conditions become favourable for the viral growth. After this when the environmental conditions are suitable for the viruses, they enter into the lytic cycle from the lysogeny and release from the bacterial cells by lysis. One of the most important enzymes for the lysis of the bacterial cells is lysine, which is secreted by the bacteriophages itself (*What are the differences between a lytic infection and a lysogenic infection? | Socratic*, no date; Broncano-Lavado *et al.*, 2021; LM and LD, 2022).

Due to the multi-drug resistant nature of several bacterial biofilms, sometimes it is extremely difficult to treat those highly pathogenic biofilm related infections or diseases with commercially available antimicrobial compounds even after using very high concentrations. So, in past few years, due to the several advantageous characteristics of bacteriophages, they attract the immense interest of several researchers towards the implication of bacteriophages in bacterial biofilm related infections or diseases control, which is known as phage therapy. Virulent phages are the most useful to eradicate bacterial biofilm for their unique characteristics such as high host specificity, self-replicating capacity, and rapid multiplication rate (Sadekuzzaman *et al.*, 2018). On other hand, lysogenic phages block the biofilm formation of several bacteria by incorporating them into the host genome. As an example, when a lysogeny phage attacks *Mycobacterium smegmati*, the phage gene Bxb1 integrates into the bacterial genome, inactivates the bacterial groE11 gene which helps in the biofilm formation in *Mycobacterium smegmati*. As a result of this inactivation, now phage infected bacterial cells can remain as planktonic cells but are unable to produce biofilm. (Resistance, 2021). In 2007, Lu et al. designed a genetically engineered bacteriophage, which can secret the enzyme DspB, which can degrade β-1,6-N-acetyl-D-glucosamine, a crucial component of biofilm formation and also needed to adhere the biofilm on a surface. After the lysis of host bacterial cells, this phage encoded enzyme can cause more degradation of surrounding biofilms and result in 99.97% of biofilm eradication (Lu and Collins, 2007; Resistance, 2021). Sometimes bacteriophages help antimicrobial compounds to enter into the bacterial biofilm by breaking the protective layers of biofilm. Many phage viruses secret several enzymes, which can degrade the extracellular polymeric substances (EPS) of bacterial biofilm, which serves as a defence barrier for the biofilm. These enzymes can also degrade the matrix proteins, capsule layers, lipopolysaccharides (LPSs), and O-polysaccharides, protecting layers of the biofilm and several bacteria and helping the bacteriophage to enter into the biofilm. Due to the clearance of protective components of the biofilm, antimicrobial compounds can also penetrate the bacterial cells and can eliminate those biofilm forming bacteria. In 2001, Hanlon et al. reported that phage can degrade the EPS matrix of *Pseudomonas aeruginosa (P. aeruginosa)* biofilm to reach the bacterial cell surface (Hanlon *et al.*, 2001; Resistance, 2021; Topka-Bielecka *et al.*, 2021). These enzymes are commonly known as phage depolymerases. In 2016, Pires et al. reported that most of these enzymes are encoded in the structural gene of the phage genome (Pires *et al.*, 2016). These enzymes are mainly classified into two groups- hydrolases and lyases. The hydrolases enzymes mainly catalyse the hydrolysis of the glycosidic bonds of the EPS layer whereas the depolymeriation done by the lyases group of enzymes does not include the usage of water (Topka-Bielecka *et al.*, 2021).

Problem arises when bacterial biofilm becomes resistant to the bacteriophage due to several reasons, such as mutations, poor phage preparation quality, etc. which restricts the entry of bacteriophages into the biofilm matrix to eradicate biofilm related infections. This problem can compensate by using combination phage therapy. This approach uses the combined implication of bacteriophage with commercially available antimicrobial compounds, other bacteriophages, chemical, and natural compounds, etc. (Topka-Bielecka *et al.*, 2021). For example, lytic bacteriophage KPO1K2 in combination with ciprofloxacin and gentamycin can eradicate *Klebsiella pneumoniae* (strain B5055) biofilm

more pronouncedly (Verma, Harjai and Chhibber, 2009; Bansal, Harjai and Chhibber, 2015). The combination therapy of phage Dep42 enzyme secreted by the bacteriophage SH-KP152226 with polymixin can effectively eradicate multi-drug resistant *Klebsiella pneumoniae* biofilm (Wu *et al.*, 2019). Another approach is to apply bacteriophage cocktail to biofilm related infections. It helps to delay the appearance of phage resistant biofilm in contrast to the single bacteriophage. Phage cocktail enhances the rate of cell lysis as well as the number of the targeted bacterial cells (Łusiak-Szelachowska, Weber-Dąbrowska and Górski, 2020). For example, bacteriophage KP34p57 in combination with lytic phage KP34, KP15, and ciprofloxacin can inhibit *Klebsiella pneumoniae* 77 biofilms more effectively compared to only KP34p57 bacteriophage (Latka and Drulis-Kawa, 2020). In 2018, Forti et al. showed a cocktail of six bacteriophages eradicate *Pseudomonas aeruginosa* isolates from clinical samples with promising effectiveness in 48 hours (Forti *et al.*, 2018; Resistance, 2021). In 2014, Alves et al. reported that *Staphylococcus aureus* biofilm can be eradicated by the combination of bacteriophage DRA88 and phage K with 100% efficiency (Alves *et al.*, 2014). Several investigation reports demonstrate that phage derived depolymerases eradicate approximately more than 92% biofilm when it is applied with chloride dioxide (ClO2) in contrast with only enzymes which can eradicate 80% biofilm (Chai *et al.*, 2014). Many research investigations reveal that natural compounds also play promising role in combinatorial phage therapy. Bacteriophage KPO1K2 and Pa29 in combination with xylitol can eradicate *P. aeruginosa* and *K. pneumonia* biofilm. It is reported that the amount of *Escherichia coli* biofilm inhibition is much greater using bacteriophage EC3a with honey, rather than using phage or honey alone (Oliveira *et al.*, 2017; Topka-Bielecka *et al.*, 2021).

5. Application of phage therapy

Due to the multi-drug resistant properties of bacteria and bacterial biofilm, it is very hard to treat those with traditional antimicrobial compounds. In the present day, antibiotic resistant bacteria is one of the major concerns to public health (Tian *et al.*, 2021). Bacteriophage therapy or combinatorial bacteriophage therapy could lit a new light to treat pathogenic or harmful bacteria and bacterial biofilm of several biofilm related infections and nosocomial infections. In table 2 we briefly discuss the various applications of phage therapy.

Table-2: Applications of bacteriophage therapy in several biofilm related infections.

Phages/Lysin	Type of Infection	Infection Model	Place of Biofilm Formation	Reference
P. mirabilis phage cocktail	Urinary tract infection	In dynamic Biofilm model	Foley catheter	(Melo *et al.*, 2016)
P. mirabilis phage cocktail	Urinary tract infection	*In vitro*	Polystyrene plate	(Maszewska *et al.*, 2018)
S. aureus phage cocktail	Oral infection	*In vitro*	Titanium surfaces	(Morris *et al.*, 2019)
S. mutants and E. faecalis single phages	Oral infection	*In vitro*	Polystyrene plate	(Szafrański, Winkel and Stiesch, 2017)
E. faecalis single phage	Oral infection	*In vitro*	Polystyrene plate	(Khalifa *et al.*, 2015)
E. faecalis single phage	Oral infection	*Ex vivo*	Root canal	(Khalifa *et al.*, 2015)

S. aureus CF-301 Lysin	Catheter-based infection	*In vitro*	Catheter tubing	(Schuch *et al.*, 2017)
S. aureus CF-301 Lysin	Joint infection	*Ex vivo*	Human synovial fluid	(Schuch *et al.*, 2017)
A. baumannii PlyF307 Lysin	Catheter-based infection	*In vitro*	Catheter	(Lood *et al.*, 2015)
A. baumannii PlyF307 Lysin	Catheter-based infection	*In vivo* mice model	Catheter sections Implanted subcutaneously	(Lood *et al.*, 2015)

6. Limitations of phage therapy

Despite the numerous success rate of phage therapy, there have been some limitations in human trials due to some major drawbacks of this technique. During phage therapy, there has a high probability to produce phage insensitive mutants (BIM) which implies many complexities in the therapy and produces phage resistant bacterial strains. Moreover, phage therapy required a diverse range of phages and high purity (Resistance, 2021). Virulent phages are more potent than lysogenic phages as sometimes bacteria acquired resistance toward lysogenic phages. So it is necessary to get a highly pure phage cocktail to able efficient eradication of bacterial biofilm. The existence of impurities such as toxins, and a mixture of different types of phages (lytic and lysogenic) could be a major drawback of phage therapy. So, it is important to avoid these conditions during the phage preparation for clinical phage therapy. Several pharmaceutical research organization develop many purification processes but none has reached that optimal threshold (Hietala *et al.*, 2019; Pires *et al.*, 2020). Another key factor of effective and efficient phage therapy is the stability of the bacteriophage. A potential phage candidate should have a good shelf life that is the effectiveness of that phage should not be dropped during the long term storage or the time of phage preparation otherwise the treatment outcome will be hampered (Merabishvili, Pirnay and De Vos, 2018; Jault *et al.*, 2019).

7. Conclusion

Several health related issues are occurred due to the infection of pathogenic bacteria and bacterial biofilm, which also facilitate the multi-drug resistant nature of bacteria. So, it is very important to eradicate or completely inhibit those biofilms to maintain healthy human health and a healthy environment. Biofilms are the accumulation of bacterial communities on solid surfaces surrounded by the EPS matrix layer. Due to this EPS matrix layer, it is very difficult to treat bacterial biofilm as this layer block the entry of several types of antimicrobial compounds and toxins. So in the last few decades, researchers are searching for new novel strategies to combat against pathogenic multi-drug resistant bacterial biofilm. In this review article, we have seen, that phage therapy could be a novel approach to treating pathogenic MDR bacterial biofilm related diseases and infections. They can eradicate or inhibit biofilm from different surfaces either by lytic or lysogenic cycle. The efficacy of bacteriophages can be enhanced by applying the bacteriophage in combination with other natural or synthetic antimicrobial compounds or other bacteriophages. Despite having several beneficial properties of phage therapy in several fields, it has many drawbacks, which sometimes limit the usage of bacteriophages to treat bacterial biofilm in the clinical treatment procedure. Future research studies should aim toward the minimization of these limitations and discover many more unknown bacteriophages to make more potent phage cocktails to inhibit bacterial biofilms more efficiently.

Conflict of Interest

The authors of this paper have no conflict of interest.

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