Review

JOURNAL OF UNIVERSITY OF BABYLON

For Pure and Applied Sciences (JUBPAS)

Vol.32; No.3.| 2024

Review of the Use of Bacteriophages in Biotechnology

Nisreen Kadum Radi[1] , Nebras Mohammed Sahi[2] , Samreh Shaker Hmood[3] , Marwah Mohammed Sahi[4] , Narges kazem Radi [5]

[1,2,3,4] College of Science for women, University of Babylon, Babylon, Iraq
[5] College of Faculty of agriculture
Email: nesreenzain.83@gmail.com

Accepted: 23/9/2024 Published: 30/9/2024

ABSTRACT

Bacteriophages are ubiquitous entities that exhibit a specialty towards one or more host strains. They are the most prevalent entities on Earth, surpassing bacteria in quantity by a factor of ten. We can identify two categories of phages: lytic and temperate. This is about phages that can add their genetic material to the host genome. This makes a prophage that copies itself inside the host cell and may protect it from other phages of the same species that might try to infect it. Alternatively, lytic phages, which are of significant importance in biotechnology, encourage the host cell to undergo lysis after their reproductive cycle. In their lysogenic state, they can disseminate genes that provide antibiotic resistance to bacteria via horizontal gene transfer. Moreover, phage therapy has garnered support from the scientific community due to its distinctive ability to address issues associated with biofilm formation and microbial regulation that other prevalent methods struggle to resolve effectively. Bacteriophages are advantageous as they offer a feasible and promising alternative. This study aims to provide the latest knowledge on the application of phages for pathogen biocontrol in industrial and healthcare environments

Key words: Bacteriophage ; gene delivery; bio preservation;food safety ; biotechnological

INTRODUCTION

The most prevalent type of viruses on Earth are called phages, or bacteriophages, and they mostly infect bacteria. First independent discoveries of them were made in 1917 in France by Félix d'Hérelle and in 1915 by Frederick Twort in England [1]. They have contributed significantly to several developments in molecular tools since their discovery. Phages were used in the famous "Waring blender experiment" by Alfred Hershey and Martha Chase to show that genes are made of DNA [2]. In addition, among other findings, phages have helped investigate the genetic regulation of enzymes, virus generation, and the mutagenesis of bacterial genes for functional investigations [3-5]. As obligatory intracellular parasites, phages are composed of a nucleic acid encased in a three-dimensional structure known as the capsid. [6-8].For a long while, the host range, morphology, and genome type of bacteriophages were the primary factors used to classify them taxonomically. Phage sizes and resistance to physicochemical agents vary, as Sir Macfarlane Burnet showed in 1937 [9]. Furthermore, in 1943, Holmes Ruska suggested a categorization of viruses using electron microscopy after observing the morphological variety of phages [10]. Based on their host range and illness symptoms, phages were grouped into three groups in this classification, also called the Holmes classification [11].A viral taxonomy based on virion features, nucleic acid content, and a Latinized nomenclature system involving many phages was proposed by Lwoff, Horne, and Tournier in 1962 [12]. David Bradley then used acridine orange staining and electron microscopy in 1967 to divide tailed bacteriophages into three groups: those with contractile tails, those with long noncontractile tails, and those with short noncontractile tails. The three morphotypes of this classification system were given the

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

names Myoviridae, Styloviridae, and Pedoviridae by Hans-Wolfgang Ackermann and Abraham Eisenstark of the Bacterial Virus Subcommittee in 1975 after the International Committee on Nomenclature of Viruses (ICNV) formally adopted it in 1971 [13–16]. The International Committee on Taxonomy of Viruses (ICTV) recognized Myoviridae and Podoviridae, as they are presently called, in 1981. In 1984, Siphoviridae made a similar move. To continue with the phage taxonomy narrative, the order Caudovirales includes the Myoviridae, Siphoviridae, Podoviridae, Ackermannviridae, and Herelleviridae families. [17].

Similarly, additional phage families, such as Inoviridae (filamentous capsid), Microviridae, Tectiviridae, Corticoviridae, Leviviridae, and Cystoviridae (polyhedral capsid) and Plasmaviridae (pleomorphic capsid), were also categorized in 1978 according to their shape [17]. But with the development of genomics, more genomic variety has been discovered by the sequencing of phage genomes, which may be found in the human gut and the deep ocean [18]. This has led to the emergence of a taxonomy based on genome structure, which includes novel subfamilies and genera as well as viral relatedness ascertained by proteome comparisons and nucleotide or shared protein sequences. In situations where there are frequent horizontal gene transfers, widely diverse genome sequences and organizations, and mosaicism, this molecular analysis technique provides a strong categorization system for phages [19–23]. National Center for Biotechnology Information (NCBI) states as[18]. Phage populations may be found in a variety of settings, including the ocean and the microbial environment inside microorganisms, as was previously described. Phage populations are essential to complex ecosystems [1]. Because of their diversity and abundance, bacteriophages are important in marine ecosystems because they affect microbial populations, encourage genetic variation, and aid in the cycling of nutrients by killing off bacteria. Phage variety is not limited to their morphology; seasonal fluctuations in the phage replicative cycle are also seen. For example, in the Canadian Arctic Shelf and the western Antarctic Peninsula, lytic infections predominate in the summer, while prophages predominate in the spring [18, 24].

LIFE CYCLES OF BACTERIOPHAGES

Regarding the characterization of phage life cycles, there are several methods for infection and release. Phage encapsidation and geographic distribution can be divided into three groups: (i) existing inside the cell and not being encapsulated. This stage can be further subdivided into three categories: (i) living inside the cell and encapsulated within fully-formed virions, which are differentiated from phage genomes and packaged only during the virion release stage; (ii) living within the cell and encapsulated. The latter category was defined by Lwoff in 1953 and includes the productive cycle against a prophage. This is the case where liberated phages are no longer detectable within their host bacterium [25,26].PPhages can exhibit a variety of infection and release tactics, leading to the development of either lytic or chronic non-temperate phages. The former describes phages that do not go through lysogenic cycles, whereas the later describes phages that are released on a continuous basis but do not show lysogenic cycles. Lytic phages go through a vegetative phase during which their DNA is assembled into mature virions before to release. Similar to this, phages that are released on a continuous basis go through a vegetative phase, but the release mechanism packages the phage's DNA into mature virions. Since these lytic and non-temperate phages may lyse the host cell and continue the cycle through the progeny that follow, they are especially intriguing for the biological control of bacteria. The earliest stage of the phage life cycle is called adsorption, and it includes the interaction of the

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

virion with the bacterium. Diffusion and non-diffuse movement are two categories into which this process can be divided, depending on whether the phages are linked to other materials. Particle shape and size are two examples of parameters that might affect the phages' migration. On the other hand, non-diffuse mobility happens when the phages attach themselves to nonhost materials and might increase the probability of coming into contact with the target bacteria if they travel in the same direction. Furthermore, virions can act as mechanical vectors and spread across greater distances through the air, dust, sprayed water, or animals. It is important to remember, nevertheless, that mass movement may not always result in contact with bacteria that are sensitive. The phage's reversible attachment to the host bacterium is the next stage in the adsorption process. Since there have been no long-term changes to the virion's morphology, this attachment is reversible. The irreversible attachment of the free virion to a bacterial cell is the final result of the adsorption process, which is made possible by secondary attachment proteins binding to the secondary receptor. The strength of this binding is greater than that of the reversible attachment, when the primary attachment protein binds to the primary receptor.The phage's acquisition of bacteria occurs in the next stage of its life cycle, when a free virion (seeds or spores for multicellular organisms) is transformed into a virocell, the "living form" of the virus. The genetic material of the virion is transferred to the bacteria's cytoplasm during this phase. Phages must get past bacterial surface features such glycocalyx, S-layers, and peptidoglycan cell walls in order to accomplish this transfer. Genome injection is the technique by which most phages introduce their nucleic acid into the host cytoplasm by use of a mix of enzymatic and mechanical mechanisms. These enzymes are specifically designed to target these structures. The phage genes are expressed and the genome replicates once within the bacterial cytoplasm, starting the process of creating new virions. The phage virions then continuously collect inside the cells until the phage causes bacterial lysis. It is noteworthy that, for phages that are chronically infected, as was previously noted, there may be a loss of infection viability or a stop in phage formation. Similar to what has been previously reported in the context of chronic, temperate, or lytic phages, the phage moves, attaches itself to the host bacteria, and trans located its genome.

STRATEGIES OF BACTERIOPHAGE ATTACK ON HOST RANGE

Phage treatment has been shown in several trials to be beneficial in treating bacterial infections in people, with a particular emphasis on treating lung infections, otitis media, and cholera. The latter, nevertheless, has not yet been the subject of a controlled clinical investigation [27]. The three main species that have been studied in these investigations are Achromobacter xylosoxidans, Staphylococcus aureus, and Pseudomonas aeruginosa. The positive outcomes of using phages to fight various illnesses have been documented by these studies. Positive results were nevertheless seen in situations when phages were the only antimicrobial therapy used [27-34]. However, it should be highlighted that not all clinical trials have shown these advantageous outcomes in comparison to conventional therapies. To treat burn wounds infected with, for instance, a phage cocktail consisting of twelve bacteriophages was found to be efficacious in one investigation.

Phage tail-like bacteriocins (PTLBs)—also called tailoring—are an additional strategy against bacterial infections. These structures resemble the tails of bacteriophages, but they are devoid of a genome and a head. Like phages, PTLBs identify and target host bacteria by attaching to receptor-binding proteins (RBPs). PTLBs, in contrast to phages, depolarize bacterial cells by

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

creating holes in their membranes. These holes let ions into the cell, which eventually causes it to die. PTLBs only function on the cell surface, in contrast to phages, which carry out their whole life cycle within the host cell. Thus, the development of bacterial resistance to PTLBs can only take place at the level of cell receptors [35].

BACTERIOPHGE AND EUKARYOTIC CELLS.

It was once thought that bacteriophages could not harm eukaryotic cells. However, new research has illuminated the dynamics between bacteriophages and eukaryotic cells, providing fresh perspectives. For example, it has been demonstrated that bacteriophages interact with mucus surfaces. T4 bacteriophages and a mucus-producing tissue cell line were used in an in vitro experiment. It was shown that the bacteriophages link to glycan residues on mucin glycoproteins through Ig-like domains found in the viral capsid protein [36]. Because of their adhesion to mucus surfaces, bacteriophages are more likely to come into contact with host bacteria, which may have an impact on the gastrointestinal microbiome and stop pathogens from colonizing the system. [36-38]. Furthermore, bacteriophages may converse with immune system cells. In one research, the bacteriophage ES2 was investigated for its effects on the expression of surface proteins CD86, CD40, and MHCII, as well as on dendritic cells' production of pro-inflammatory cytokines such as IL-6, IL-1α, IL-1β, and TNF-α. The results showed that pro-inflammatory cytokines and surface proteins were expressed more when ES2 was present. The study also showed that NF-κBp65 was activated and translocated to the nucleus, which triggered the NF-κB signaling pathway [39]. In a similar vein, two Escherichia coli bacteriophages were used to produce TNF-α, and the activation status of mammalian macrophages was examined in that investigation as well.

Applications of Phages in Livestock and Food Industry

The use of bacteriophages in biotechnology has produced a wide range of varied and constantly growing applications from the point of giving phages directly to living animals to the point of combining them into ready-to-eat food. Bacteriophages have been the subject of much research and study in addition to their intended use in the food business, particularly in the areas of health and sanitary treatment [40-46].

Applications in Live Animals (Animals Phage Therapy)

Ensuring food safety in agricultural settings and other settings that involve animal husbandry is essential for preserving public health. Numerous animals are frequently housed in these settings, most of them being restricted. Regrettably, the animal herds may become infected with new illnesses as a result of this confinement. These animals then serve as reservoirs for zoonotic bacterial infections, which can infiltrate the food chain and infect people, potentially leading to death. In light of this, employing bacteriophages to manage infections in animals becomes a practical choice. Animals can be given bacteria in a number of ways, such as by oral intake, intragastric injection, bacteriophage suspensions directly injected into food and drink, suspension application, through the muscle, transdermal, subcutaneous, and epidermal injections. Food goods such as meat, dairy, processed meals, fruits, vegetables, and food packaging can all be affected by bacteriophe. Bacterial populations are eliminated when lytic phages are applied to food. In a different technique called biofilm disaggregation, bacteria produce extracellular

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

polymeric matrix (EPS), which serves as a binding agent and enables the biofilm to adhere to solid and biological surfaces in food storage apparatus and structures.

Biofilm Disaggregation Biofilms complex

communities of microbes that may produce a wide variety of extracellular polymeric matrix (EPS), including nucleic acids, proteins, lipids, and polysaccharides [47]. This extracellular polymer forms the biofilm into a three-dimensional conformation. It functions as a binding agent, allowing the biofilm to adhere to solid surfaces like those found in product storage structures and food industry equipment, as well as biological surfaces like those of meat, vegetables, fruits, and other foods. [48-50]. The biofilm's bacteria use the polymeric matrix to draw nutrients and energy from particles and dissolved materials in the surrounding media. The matrix also offers defense against oxidation, dehydration, certain antibiotics, UV rays, and other dangerous substances [49]. While biofilms have demonstrated encouraging biotechnological uses, including the capacity to filter potable water, break down solid waste and wastewater, and create chemicals and biofuels [51], they also give rise to problems in a number of other domains, including industry, the environment, and medicine. Within the medical area, biofilms are linked to the internal and exterior contamination of implants and medical equipment, which can result in the development of infectious illnesses and pose serious hazards to human health [52,53]. Foodborne pathogens remain on surfaces that come into touch with food and inside biofilms, which causes a decline in food quality, quantity, and safety in the food business [50].

Enzybiotics

Apart from the aforementioned tactics, there exist substitute methods that circumvent the direct involvement of phages and instead concentrate on exploiting the enzymes that they encode. An example of one such method is the use of endolysins, hydrolase enzymes that are able to cleave the peptidoglycan linkages found in the bacterial cell wall. Endolysins can be used to release freshly generated viral particles, which will ultimately cause the bacteria and the biofilm structure to degrade [54-56]. It is significant to remember that endolysins may be categorized into several groups according to their enzymatic activity, which is dictated by the particular kind of peptidoglycan bond that they can break[57]. Furthermore, lysozymes—like the phage T4 gp5 protein—function by combining with the host's outer membrane and breaking down the peptidoglycan layer. After the peptidoglycan layer breaks down, the nucleocapsid enters the host cytoplasm and starts the mechanisms that eventually cause cell lysis [58-60].

Biosensor

Because of their exceptional sensitivity, bacterial detection techniques based on culture are commonly acknowledged as the gold standard. Nevertheless, the disadvantage of these approaches is that the microbiological detection tests take a long time to complete. Thus, it is important to investigate new methods that may address these drawbacks in order to save testing time and expense while maintaining the critical features of reliability, sensitivity, and specificity in a variety of applications. As a result, scientists are now focusing on novel methods of identifying bacteria, such as mass spectrometry sensors, immunity-based sensors (such the enzyme-linked immunosorbent assay, or ELISA), and polymerase chain reaction (PCR) [61,62]. Biosensors are comprised of a transducer, an electrical system that amplifies, analyzes, and displays the signal, and a biological recognition component.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

Phage Development for Vaccines

The inherent qualities of these organisms make them suitable candidates for the role of vaccine delivery vehicles, and this article will discuss phages as such. The ease of large-scale phage production in bacterial host organisms, the simplicity of genetic modification, the phages' high stability in unfavorable environments and conditions, the stability and immunogenicity of the displayed antigens, and their capacity to induce humoral and cellular immunity are among the phage characteristics that make them particularly valuable for the development of vaccines [[63-66].Phages can be utilized to produce vaccinations against phage DNA and phage display.[66] .

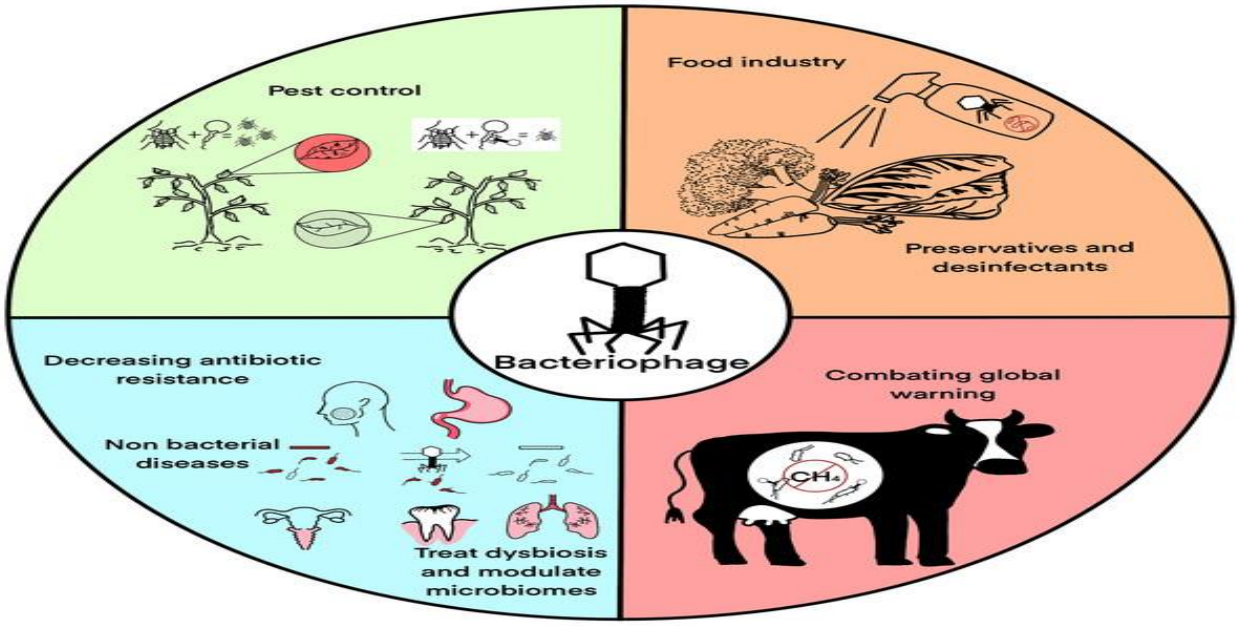

Figure 1: Main bacteriophage applications: pest control, food industry, medical applications excluding classical phage therapy, and global warming mitigation.
Confluent of interest: no Confluent of interest [67].

ACKNOWLEDGMENT

The author wishes to express gratitude to all the researchers involved in this paper who have contributed data to the scientific community.

Conflict of interests.

There is no conflict interest

References

1. M.R.J.Clokie ; A.D.Millard ; Letarov, A.V.; Heaphy, S. “Phages in Nature”. *Bacteriophage* ,vol. 1,no. 31–45,2011
2. A.D.Hershey ; M.Chase.“Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage”. *J. Gen. Physiol*. Vol. 36,. 39–56,1952.
3. N.Kleckner ; J. Roth; D.Botstein . “Genetic Engineering In Vivo Using Translocatable Drug-Resistance Elements. New Methods in Bacterial Genetics” . *J. Mol. Biol.* Vol.116, 125–159,1977.

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

4. B.Wasylyk ; R.Derbyshire ; A. Guy; D.Molko ;A.Roget ; R.Téoule ; P. Chambon ."Specific in Vitro Transcription of Conalbumin Gene Is Drastically Decreased by Single-Point Mutation in T-A-T-A Box Homology Sequence ". *Proc. Natl. Acad. Sci. USA* ,vol. 77, 7024–7028,1980.
5. F.Jacob ; J.Monod . "Genetic Regulatory Mechanisms in the Synthesis of Proteins". *J. Mol. Biol*. Vol. 3, 318–356,1961.
6. L.K.Harada ; E.C. Silva;W.F. Campos;F.S. del Fiol; M. Vila; D , ; V.N.Krylov ; V.M.Balcão. "BiotechnologicalApplications of Bacteriophages: State of the Art". *Microbiol. Res.* Vol. 212–213, 38–58,2018.
7. K.D.Seed ; D.W. Lazinski; S.B. Calderwood; A. A. Camilli ".Bacteriophage Encodes Its Own CRISPR/Cas Adaptive Response to Evade Host Innate Immunity". *Nature* , 494, 489–491,2013.
8. Ye, M.; Sun, M.; , D. Huang; Z.Zhang; H.Zhang ; S. Zhang ; F.Hu ; X. Jiang ; W. A Jiao."Review of Bacteriophage Therapy for Pathogenic Bacteria Inactivation in the Soil Environment". *Environ. Int*. Vol. 129, 488–496,2019.
9. F.M.Burnet. "The Classification of Dysentery-Coli Bacteriophages. III. A Correlation of the Serological Classification with Certain Biochemical Tests". *J. Pathol. Bacteriol*. Vol. 37, 179–184,1933.
10. Haq, I.U., Chaudhry, W.N., Akhtar, M.N. et al. "Bacteriophages and their implications on future biotechnology: a review". *Virol J* ,vol.9, 9 ,2012.
11. A.Lwoff ; R. Horne ; P. A. "Tournier.System of Viruses. Cold Spring Harb". *Symp. Quant. Biol*. vol. 27, 51–551962,.
12. D.E.Bradley. "Ultrastructure of Bacteriophage and Bacteriocins. Bacteriol". *Rev*. Vol. 31, 230–314,1967.
13. D.E.Bradley. "The Fluorescent Staining of Bacteriophage Nucleic Acids". *J. Gen. Microbiol.* Vol. 44, 383–391,1966.
14. D.E.Bradley. "The Structure of Coliphages". *J. Gen. Microbiol.* Vol.31, 435–445,1963.
15. H.W.Ackermann ; A.Eisenstark. "The Present State of Phage Taxonomy". *Intervirology* ,vol. 3, 201–219,1974.
16. D.Turner; A.M.Kropinski ; E.M.Adriaenssens. "A Roadmap for Genome-Based Phage Taxonomy". *Viruses* ,vol. 13, 506 ,2021.
17. M.B.Dion ;F.Oechslin ; S.Moineau. 'Phage Diversity, Genomics and Phylogeny'. *Nat. Rev*. ,vol. 18, 125–138,2020.
18. R.Lavigne; D.Seto ; P.Mahadevan; H.W.Ackermann; A.M.Kropinski. "Unifying Classical and Molecular Taxonomic Classification: Analysis of the Podoviridae Using BLASTP-Based Tools". *Res. Microbiol.vol.* 159, 406–414,2008.
19. R.Lavigne; P. Darius; E.J.Summer; D. Seto ; P. Mahadevan; A.S. Nilsson ;H.W.Ackermann ; A.M.Kropinski. 'Classification of Myoviridae Bacteriophages Using Protein Sequence Similarity". *BMC Microbiol*. Vol. 9, 9,2009.
20. E.M.Adriaenssens ;R.Edwards ;J.H.E. Nash; P.Mahadevan ; D.Seto ; H.W. Ackermann; R. Lavigne; A.M.Kropinski. "Integration of Genomic and Proteomic Analyses in the Classification of the Siphoviridae Family". *Virology* , 477, 144–154,2015.
21. D.Paez-Espino ; E.A.Eloe-Fadrosh; G.A.Pavlopoulos ; A.D. Thomas; M.Huntemann ; N. Mikhailova; E.Rubin ; N.N.Ivanova ; N.C.Kyrpides.' Uncovering Earth's Virome". *Nature* , 536, 425–430,2016.
22. F.Rohwer; R.Edwards. "The Phage Proteomic Tree: A Genome-Based Taxonomy for Phage". *J. Bacteriol*. , 184, 4529–4535,2002.
23. C.A. Suttle."Marine Viruses—Major Players in the Global Ecosystem". *Nat. Rev. Microbiol*. Vol. 5, 801–812,2007.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

24. D.Dams; L.Brøndsted; Z.Drulis-Kawa; Y.Briers. "Engineering of Receptor-Binding Proteins in Bacteriophages and Phage Tail-like Bacteriocins. Biochem".*Soc.Trans*., 47, 449–460,2019 .
25. W.C.Summers. "Cholera and Plague in India: The Bacteriophage Inquiry of 1927–1936". *J. Hist. Med.* Vol.48, 275–301,1993.
26. H.S.Abul-Hassan ; k.El-Tahan. Massoud, B.; Gomaa, R. "Bacteriophage Therapy of Pseudomonas Burn Wound Sepsis". *Ann. MBC* vol. 3, 262–264,1990.
27. C.Essoh; Y.Blouin ; G.Loukou ; A.Cablanmian ; S.Lathro ; E. Kutter ; V.H.Thien ; G.Vergnaud ; C.Pourcel. "The Susceptibility of Pseudomonas Aeruginosa Strains from Cystic Fibrosis Patients to Bacteriophages". *PLoS ONE* , 8, e60575,2013.
28. N.Hoyle ; P.Zhvaniya ;N. Balarjishvili ; D.Bolkvadze ; L.Nadareishvili ; D. Nizharadze; J. Wittmann; C.Rohde ; M.Kutateladze. "Phage Therapy against Achromobacter Xylosoxidans Lung Infection in a Patient with Cystic Fibrosis: A Case Report". *Res. Microbiol.* 169, 540–542,2018.
29. P.Jault; T.Leclerc ; S.Jennes ; J.P.Pirnay ; Y.A. Que; G.Resch ; A.F. Rousseau; F. Ravat; H.Carsin ; R.le Floch ; et al. "Efficacy and Tolerability of a Cocktail of Bacteriophages to Treat Burn Wounds Infected by Pseudomonas Aeruginosa (PhagoBurn): A Randomized, Controlled, Double-Blind Phase 1/2 Trial". *Lancet Infect. Dis*. 19, 35–45,2019.
30. L.Kvachadze ; N.Balarjishvili ; T.Meskhi ; E.Tevdoradze ; N. Skhirtladze; T. Pataridze; R. Adamia;T. Topuria ;E. Kutter; C.Rohde ; et al. "Evaluation of Lytic Activity of Staphylococcal Bacteriophage Sb-1 against Freshly Isolated Clinical Pathogens". *Microb. Biotechnol*. Vol. 4, 643–650,2011.
31. K. Markoishvili; G.Tsitlanadze ; R.Katsarava ; J.Glenn Morris ; A.Sulakvelidze ; C.Alexander Sulakvelidze. "Pharmacology and Therapeutics A Novel Sustained-Release Matrix Based on Biodegradable Poly(Ester Amide)s and Impregnated with Bacteriophages and an Antibiotic Shows Promise in Management of Infected Venous Stasis Ulcers and Other Poorly Healing Wounds". *Int. J. Dermatol.* Vol. 41, 453–458,2002.
32. D.D. Rhoads; R.D. Wolcott; M.A.Kuskowski ; B.M. Wolcott; L.S. Ward ; A. Sulakvelidze."Bacteriophage Therapy of Venous Leg Ulcers in Humans: Results of a Phase I Safety Trial". *J. Wound Care* ,vol. 18, 237–243,2009.
33. J.J.Barr ; R.Auro ; M.Furlan ; K.L. Whiteson ; M.L.Erb ; J. Pogliano ; A. Stotland; R. Wolkowicz; A.S. Cutting; K.S. Doran; et al. "Bacteriophage Adhering to Mucus Provide a Non-Host-Derived Immunity". *Proc. Natl. Acad. Sci. USA* , vol.110, 10771–10776,2013.
34. J.J.Barr ; R. Auro; N.Sam-Soon ; S.Kassegne ; G. Peters ; N. Bonilla ; M. Hatay; S. Mourtada; B.Bailey; M. Youle ; et al. "Subdiffusive Motion of Bacteriophage in Mucosal Surfaces Increases the Frequency of Bacterial Encounters". *Proc. Natl. Acad. Sci. USA* , 112, 13675–13680,2015.
35. E. Guerin ; C.Hill. "Shining Light on Human Gut Bacteriophages". *Front. Cell. Infect. Microbiol*. Vol.10, 481,2020.
36. T.W. An; S.J.Kim ; Y.D.Lee; J.H.Park ; H.I.Chang. "The Immune-Enhancing Effect of the Cronobacter Sakazakii ES2 Phage Results in the Activation of Nuclear Factor-KB and Dendritic Cell Maturation via the Activation of IL-12p40 in the Mouse Bone Marrow". *Immunol. Lett*. , 157, 1–8,2014.
37. A.V.Corpuz. "Potential of Bacteriophage Therapy in Treating Hospital Wastewater". *Eur. J. Mol. Clin. Med.* Vol. 7, 2020.
38. E.Ballesté ;A.R.Blanch ; M.Muniesa ; C. García-Aljaro; L.Rodríguez-Rubio ; J.Martín-Díaz ; M.Pascual-Benito ; J.Jofre. "Bacteriophages in Sewage: Abundance, Roles, and Applications". *FEMS Microbes* , 3, xtac009,2022.
39. Z.Guo; H. Lin; X.Ji ; G.Yan; L.Lei ; W. Han; J. Gu; J. Huang."Therapeutic Applications of Lytic Phages in Human Medicine". *Microb. Pathog*. Vol.142, 104048,2020.

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

40. L. Qin; M.Huiwen; J. Wang; Y.Wang ; S.A. Khan; Y.Zhang ; H.Qiu; L. Jiang; L.He ; Y. Zhang; et al. "A Novel Polymerase β Inhibitor from Phage Displayed Peptide Library Augments the Anti-Tumour Effects of Temozolomide on Colorectal Cancer". *J. Chemother.*, 34, 391–400,2021.
41. T.Yan ; L. Liang; P.Yin; Y.Zhou; A.M.Sharoba; Q. Lu; X.Dong; K. Liu; I.F. Connerton ; J.Li. "Application of a Novel Phage LPSEYT for Biological Control of Salmonella in Foods". *Microorganisms* , 8, 400,2020.
42. D.E. Waturangi; C.P.Kasriady ; G.Guntama ; A.M.Sahulata ; D.Lestari ; S.Magdalena. "Application of Bacteriophage as Food Preservative to Control Enteropathogenic Escherichia Coli (EPEC)". *BMC Res. Notes* ., 14, 336,2021.
43. M.S. Islam ; X.Yang ; C.W.Euler ; X.Han ; J. Liu; M.I. Hossen; Y. Zhou; J. Li."Application of a Novel Phage ZPAH7 for Controlling Multidrug-Resistant Aeromonas Hydrophila on Lettuce and Reducing Biofilms". *Food Control* , 122, 107785,2021.
44. M.E. Cortés; J.Consuegra Bonilla ; R.D.Sinisterra. "Biofilm Formation, Control and Novel Strategies for Eradication. Sci. Against Microb". *Pathog. Commun. Curr. Res. Technol. Adv*. Vol. 2, 896–905,2011.
45. H.C. Flemming; J. Wingender;U.Szewzyk ; P. Steinberg; S.A. Rice; S.Kjelleberg. "Biofilms: An Emergent Form of Bacterial Life. Nat. Rev. Microbiol". vol. 14, 563–575,2016.
46. Flemming, H.;Wingender,J."The Biofilm Matrix". *Nat. Rev. Microbiol*. Vol. 8, 623–633,2010.
47. S. Satpathy; S.K.Sen ; S.Pattanaik ; S.Raut. "Review on Bacterial Biofilm: An Universal Cause of Contamination". *Biocatal. Agric. Biotechnol.* Vol. 7, 56–66,2016.
48. B. Halan; K.Buehler ; A.Schmid. "Biofilms as Living Catalysts in Continuous Chemical Syntheses". *Trends Biotechnol*. Vol.30, 453–465,2012.
49. C.Bordi; S.de Bentzmann. "Hacking into Bacterial Biofilms: A New Therapeutic Challenge". *Ann. Intensive Care* .vol. 1, 1–8. Viruses ,vol. 15, 349 2 ,2011.
50. M.Shirtliff; J.G.Leid. "The Role of Biofilms in Device-Related Infections"; Shirtliff, M., Leid, J.G., Eds.; Springer: Berlin/Heidelberg, Germany, Vol. 3, ISBN 978-3-540-68113-7,2009.
51. D.B. Gilmer; J.E. Schmitz; C.W. Euler; V.A. Fischetti.Novel Bacteriophage Lysin with Broad Lytic Activity Protects against Mixed Infection by Streptococcus Pyogenes and Methicillin-Resistant Staphylococcus Aureus. Antimicrob. Agents Chemother. 2013, 57, 2743–2750.
52. U.Sharma ; A.Vipra ; S. Channabasappa.Phage-Derived Lysins as Potential Agents for Eradicating Biofilms and Persisters. Drug Discov. Today 2018, 23, 848–856.
53. R.Vázquez; E.García ; P.García. Phage Lysins for Fighting Bacterial Respiratory Infections: A New Generation of Antimicrobials. Front. Immunol. 2018, 9, 2252.
54. D.Nelson; L.Loomis ; V.A.Fischetti. Prevention and Elimination of Upper Respiratory Colonization of Mice by Group A Streptococci by Using a Bacteriophage Lytic Enzyme. Proc. Natl. Acad. Sci. USA 2001, 98, 4107–4112.
55. D.H. Bamford; M.Romantschuk ; P.J.Somerharju. Membrane Fusion in Prokaryotes: Bacteriophage Phi 6 Membrane Fuses with the Pseudomonas Syringae Outer Membrane. EMBO J. 1987, 6, 1467–1473.
56. J.Caldentey ; D.H.Bamford. "The Lytic Enzyme of the Pseudomonas Phage B6. Purification and Biochemical Characterization". Biochim. Biophys. Acta (BBA)—*Protein Struct. Mol. Enzymol.* Vol. 1159, 44–50,1992.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

57. L. Mindich; J. Lehman."CellWall Lysin as a Component of the Bacteriophage C6 Virion". *J. Virol.* Vol. 30, 489–496,1979.
58. M. Romantschuk ; V.M.Olkkonen ; D.H.Bamford. "The Nucleocapsid of Bacteriophage 06 Penetrates the Host Cytoplasmic Membrane ". *EMBO J.vol.* 7, 1821–1829,1988.
59. U.Farooq ; Q.Yang ; M.W.Ullah ; S.Wang. "Bacterial Biosensing: Recent Advances in Phage-Based Bioassays and Biosensors". *Biosens. Bioelectron*. Vol.118, 204–216,2018.
60. L.Richter ; M.Ritchter-Janczuk ; J. Niedziółka-Jönsson; J. Paczesny; R.Hołyst. "Recent Advances in Bacteriophage-Based Methods for Bacteria Detection". *Drug Discov. Today* , vol.23, 448–455,2018.
61. S.Adhya ; C.Merril ; B.Biswas. "Therapeutic and Prophylactic Applications of Bacteriophage Components in Modern Medicine". *Cold Spring Harb. Perspect. Med.* Vol. 4, a012518,2018.
62. K.A.Henry ; M.Arbabi-Ghahroudi ; J.K.Scott. "Beyond Phage Display: Non-Traditional Applications of the Filamentous Bacteriophage as a Vaccine Carrier, Therapeutic Biologic, and Bioconjugation Scaffold". *Front. Microbiol.* Vol. 6, 755,2015.
63. J.Nicastro ; K.Sheldon; R.Slavcev. "Bacteriophage Lambda Display Systems: Developments and Applications". *Appl. Microbiol. Biotechnol*. Vol. 98, 2853–2866,2014.
64. T.I. Samoylova; A.M.Cochran ; A.M.Samoylov ; B. Schemera; A.H. Breiteneicher; S.S. Ditchkoff; V.A.Petrenko ; N.R.Cox. "Phage Display Allows Identification of Zona Pellucida-Binding Peptides with Species-Specific Properties: Novel Approach for Development of Contraceptive Vaccines for Wildlife". *J. Biotechnol*. 162, 311–318,2012.
65. R.S. Lopes; M.A.F. Queiroz; S.T.M. Gomes ; A.C.R.Vallinoto ; L.R. Goulart; R.Ishak. "Phage Display: An Important Tool in the Discovery of Peptides with Anti-HIV Activity". *Biotechnol. Adv*.vol. 36, 1847–1854, 2018.
66. L. Aghebati-Maleki; B. Bakhshinejad ; B.Baradaran ; M.Motallebnezhad; A.Aghebati-Maleki; H. Nickho; M.Yousefi; J.Majidi." Phage Display as a Promising Approach for Vaccine Development". *J. Biomed. Sci*.vol. 23, 66,2016.
67. K.A.Noren ; C.J.Noren. "Construction of High-Complexity Combinatorial Phage Display Peptide Libraries". *Methods*, vol. 23, 169–178,2001.
68. JC.García-Cruz; D.Huelgas-Méndez; JS.Jiménez-Zúñiga; X.Rebollar-Juárez; M.Hernández-Garnica ; AM. Fernández-Presas; FM.Husain; R.Alenazy, M.Alqasmi , T.Albalawi, P.Alam , R.García-Contreras . "Myriad applications of bacteriophages beyond phage therap". *PeerJ* .11:e15272 ,2023.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

الخلاصة

تُعد العاثيات (البكتريوفاجات) كيانات منتشرة في كل مكان وتظهر تخصصًا تجاه سلالة أو أكثر من العوائل. وهي الكيانات الأكثر انتشارًا على الأرض، حيث تفوق في عددها البكتيريا بعشرة أضعاف. يمكننا تصنيف العاثيات إلى فئتين: العاثيات الحالّة والعاثيات المعتدلة. تتعلق هذه الدراسة بالعاثيات التي يمكنها إضافة مادتها الوراثية إلى جينوم العائل، مما يشكل طليعة العاثية (بروفاج) التي تنسخ نفسها داخل خلية العائل وقد تحميها من العاثيات الأخرى من نفس النوع التي قد تحاول إصابتها. من ناحية أخرى، تحث العاثيات الحالّة، التي لها أهمية كبيرة في التكنولوجيا الحيوية، خلية العائل على التحلل بعد دورة تكاثرها. في حالتها اللايتوجينية، يمكن أن تنشر الجينات التي تمنح البكتيريا مقاومة للمضادات الحيوية عبر النقل الجيني الأفقي. علاوة على ذلك، حصل العلاج بالعاثيات على دعم من المجتمع العلمي بسبب قدرته الفريدة على معالجة المشكلات المرتبطة بتكوين الأغشية الحيوية وتنظيم الميكروبات، والتي تكافح الأساليب السائدة الأخرى في حلها بفعالية. تُعد العاثيات مفيدة لأنها توفر بديلاً ممكنًا وواعدًا. تهدف هذه الدراسة إلى تقديم أحدث المعارف حول تطبيق العاثيات للتحكم البيولوجي في مسببات الأمراض في البيئات الصناعية والرعاية الصحية

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652