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LETTER TO THE EDITOR

Bacteriophage therapy- a refurbished age-old potential strategy to treat antibiotic and multidrug resistant bacterial infections in future

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Abstract
The worldwide prevalence of antimicrobial resistance coupled with the unavailability of newer antibiotics, has brought the sharp focus back among the scientific community, towards the discovery of novel alternative therapeutics to tackle the menace. Consequently, in the current post-antibiotic era, 'Bacteriophage Therapy' has emerged as one of the most promising option to address this problem. Bacteriophages, actually discovered long back, has shown greater potential to kill various bacterial pathogens, including the resistant clinical ones. Some of the other advantages for the use of bacteriophage therapy to treat infectious diseases include, wider availability of these microorganisms in nature, host-specific action, absence of any significant side-effects in humans and most often also exhibiting a broader anti-bacterial potential. In the recent times, the potential of phage therapy has been demonstrated in various treatments, clinical trials and infection models across the globe, where even antibiotics have completely failed. To address the global threat of AMR, WHO and UN have jointly illustrated "One Health" approach, recently extending the context to bacteriophage therapy. Many pharmaceutical companies have also recently started employing bacteriophages for developing different kinds of formulations for catering to medical and other industries. It has even shown great effect as combinatorial therapy along with antibiotics, to treat or manage various critical antibiotic resistant clinical infections. This continuously expanding potential of the bacteriophages holds great promise in the future, in the fight against the rising threat of AMR globally.

Background

The reports of increasing antimicrobial resistance globally, coupled with limited discovery of new antibiotics necessitated the need among scientists to generate novel solutions to tackle the threat. It is estimated that antibiotic and multi drug resistant (MDR) bacterial infections would cause 700,000 deaths globally each year on an average, soon. This is expected to even rise to approximately 10 million deaths annually by 2050, if the present state of affairs continues unchecked [1]. There are instances of extensive use of antibiotics such as monosins and salinomycin in food industry, mainly as animal feed, in addition to the already sizeable proportion in use for human therapeutics. Some groups of antibiotics like Isoniazide, are reserved for specialized diseases like tuberculosis, though exhibiting decreasing effect. Antibiotics such as tetracycline and streptomycin are mainly used for agriculture setting to treat bacterial infections in plants. So, this illustrates that antibiotics have routinely been over exploited in the sphere of 'human-animal-plant' health.

To address the global threat of AMR (Antimicrobial Resistance), WHO (World health organization) and UN (United Nations) illustrated "One Health" approach, where AMR is linked to three different verticals (Animal, Human and Environment), linked to the monitoring of the irresponsible and excessive use of the antibiotics. This approach has previously been applied to 'Antibiotic Stewardship' and recently also extended to the context of 'Bacteriophage Therapy', one of the age-old and potential alternatives to overcome AMR [2, 3]

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Bacteriophage therapy to treat antimicrobial resistant infections

Due to the increasing trend of antimicrobial resistance, it is an urgent requirement to develop novel antimicrobial therapies. In the Post-antibiotic era, where antibiotics have mostly failed, 'Bacteriophage Therapy' exhibits as one of the most promising and viable therapeutic option, among the various alternatives for addressing the problem. There are many advantages of bacteriophages as compared to antibiotics usage, and thus specific bacteriolytic phages can be considered as one of the potential therapeutic options in the future (Fig. 1).

Bacteriophage therapy, though initially discovered by Frederick William Twort, an English bacteriologist in 1916, it was initially practiced on a wide scale in the erstwhile Soviet Union around 1930s for the treatment of a variety of clinical infections [4]. Later it has shown greater promise, in killing even the antibiotic-resistant bacterial pathogens, by overcoming their rising resistance. One of the pioneering and ground-breaking work in this area of bacteriophage therapy, has also been of the French microbiologist, Félix d'Hérelle. He discovered these unknown species of bacteria engulfing viruses through his independent research in 1917, and coined the term 'bacteriophages' for them. In the next couple of years he discovered different species of bacteriophages, specific for particular bacterial pathogens and also demonstrated the effectiveness of these in treating critical infections in different organisms including plants, animals and humans. But unfortunately the value of it was somehow lost with the discovery of 'antibiotics'. Some of the unique factors which have worked to the advantages of the bacteriophages are its wider availability from various natural resources, host specificity, broader anti-bacterial potential,

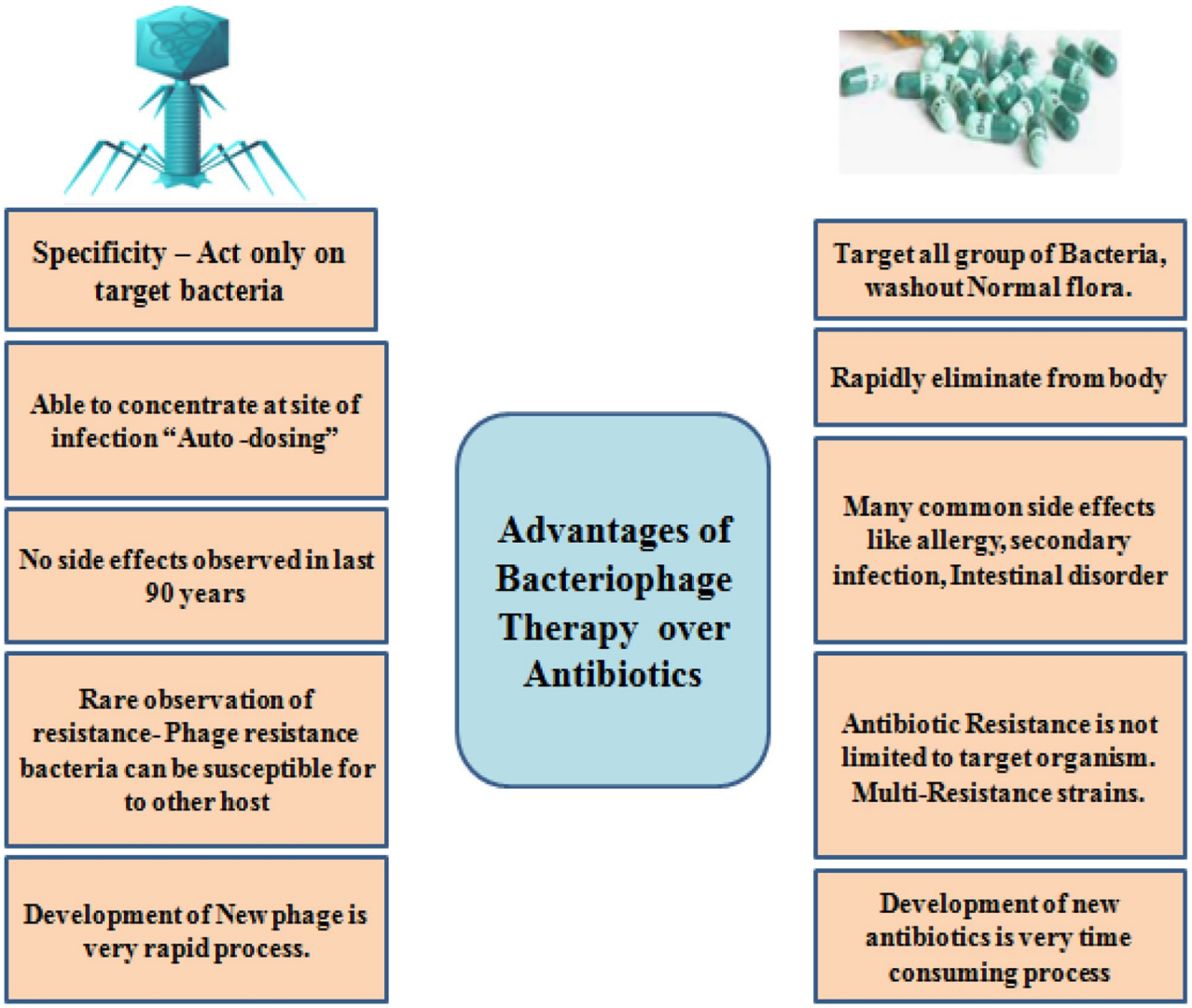

Fig. 1 Advantages of Bacteriophage therapy over Antibiotics

along with and minimal side effects in higher species, including animals and humans [5].

In the recent times, the power of phage therapy has been exhibited outside the routine laboratory experiments, specifically in various clinical trials for infection models as well as directly in therapeutic applications, to treat critical infection in patients. It assumes greater prominence, as other conventional forms of treatment including the administration of antibiotics, have failed to a large extent for curing these infections in the patients [6].

Enzybiotics– phage encoded proteins

Recently phage derived proteins have elicited interest because of their fast and unique mechanism of action. Particularly the use of these phage proteins, without the nucleic acid component, increases their specificity against the bacterial pathogens, also minimizing the chances of resistance development in the bacteria. It comprises of mainly two classes of enzymes, 'Lysin' which is also known as Peptidoglycan hydrolases and 'Polysaccharide depolymerases'. Lysin enzyme degrade the bacterial cell wall and depolymerases can efficiently break down the bacterial exopolysaccharides, which is mainly responsible for the biofilm formation [7]. Lysin has exhibited rapid bactericidal activity against Methicillin resistant *S. aureus* infection, just in 3 h. This illustrated that even a phage enzyme can exhibit significant and fast antibacterial action, almost as efficiently as the complete phage particle itself [8].

Recent records of clinical trials

There are a number of clinical trials which have been already completed and few ongoing, which can be successfully launched as effective phage therapies in the market in future (Table 1). To highlight a few, 'PhagoBurn' has launched one of the largest multicentre, randomized and controlled phase I/II clinical trials in 2013, which involved 27 patients who were suffering from *P.aeruginosa* wound infections after burning incidents. The patients were recruited both at hospitals in France and Belgium simultaneously and randomly administered a cocktail of 12 different lytic phages. The phage efficacy was compared with a standard '1% sulfadiazine silver emulsion cream'. Both treatments were followed until 14 days. It was found that application of phages were able to significantly decrease bacterial infections, as compared to the 1% sulfadiazine silver emulsion cream, along with no side effects [9].

In 2019, 'Phage National Network' and 'Bio-bank of Bacteriophages' in Australia, had successfully coordinated to treat a serious case of acute MDR bacterial infection in a 7-year-old Indian origin girl, developed as a result of post-surgical complication. She was a victim of a critical car accident resulting in multiple fractured bones. This was indeed one of the landmark applications of 'Phage therapy' to treat serious and incurable resistant infections in humans [10].

Banaras Hindu University in India had launched a randomized, placebo controlled double blind clinical trial from 2021 to 2023, for using Bacteriophages to treat chronic wound infections. A total of 30 patients were involved in the study who were suffering from the same. Phage cocktail and placebo were applied in alternate days, till a total of 39 days.

Table 1 Bacteriophage based controlled clinical trials in human

Location	Title	Year of study	Disease	Intervention	Status
United – [32] kingdom	A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic– resistant *Pseudomonas aeruginosa*	2009	Chronic otitis	*P.aeruginosa* phage preparation	Completed
France [1]	Bacteriophage effect on *Pseudomonas aeruginosa*	2013	Cystic fibrosis	Induced sputum to evaluate efficacy of bacteriophages	Completed
Denmark [3]	The role of phages in microbial gut ecology: A study of interactions between antibiotics and the gut microbiota	2013–2014	Healthy individual, enrolled as a volunteer	Single blind, randomised controlled trial	Completed
France, [1,3] Belgium, Switzerland	Evaluation of phage therapy for the treatment of *Escherichia coli* and *Pseudomonas aeruginosa* wound infection in burn patients.	2013–2017	Chronic wound infection	*E-coli* and *P.aeruginosa* cocktail + Silver sulfadiazine as a control	Completed
Portugal[2]	Chronic ulcers	2018	Chronic ulcer	Diabetic wound infection treatment through phage	Ongoing–phase I

[1]Clinical Trials.gov (https://clinicaltrials.gov/)

[2]Technophage.pt (https://technophage.pt/index.php/r-d/product-pipeline)

[3]Clinicaltrialsregister.ed (https://www.clinicaltrialregister.eu/ctr-search/search)

The result was quite promising with 93.3% wound healing in patients by 39 days and almost complete clearing of the infections by 90 days in the patients receiving the phage therapy, whereas in contrast, patients who received the placebo instead of the bacteriophages, exhibited almost 83% bacterial infections intact during the same time. There was also no side effects observed from the phage therapy. So, this study completely established the fact that Phage therapy induced significant improvement in acute wound infections in clinical studies [11–13].

In July 2022, The National Institutes of Health (NIH, USA) initiated a clinical trial in partnership with 'The Walter Reed Army Institute of Research and Adaptive Phage Therapeutics', USA, aiming to enrol approximately 30–40 patients in a Phase-II clinical trial. The goal of this trial was to assess the safety and efficacy of phage therapy in cystic fibrosis patients suffering from secondary multi-drug resistant *Pseudomonas aeruginosa* infection, due to the colonization of the patients' lungs with the pathogens. This was in continuation of a successful Phase-I Trial [14].

A review published in the "The Lancet Infectious Disease' in 2022, comprised of data from totally of fifty-nine clinical studies, which included the employment of phage therapy for treating various human infections. It significantly showed that out of totally 1904 patients included in the trails, who were lodged in various hospitals and suffering from chronic drug-resistant infections, approximately 79% exhibited remarkable progressive improvement in the disease condition, post treatment with the phages [15].

Recently, researchers of San Diego's School of Medicine at the University of California were able to effectively cure a multi-drug resistant *Pseudomonas aeruginosa* infection, linked to a 'recalled' brand of eye drops [16].

Commercial products

Currently there are already many phage-based products being used as prophylactic measure to remove pathogenic bacteria in horticulture and animal food industries, with no noticeable side-effects. Bacteriophages have also found diagnostic application as 'Pathogen Detection Test Kit', which has received regulatory approval to be used for screening drug resistant bacterial infections (Table 2).

Phage bank

Recently, the first Phage Bank of the world has been opened in UK, with the sole aim to preserve the different potential strains of the bacteriophages capable of therapeutic applications. It is a landmark occasion and according to its Director, Prof. Martha Clokie, from the University of Leicester, the future clinical application of these phages might help to cure critical conditions in patients such as diabetic foot ulcers and chronic urinary tract infections. Further, the

Table 2 Commercial Bacteriophage-based products

Product	Description	Specific target	Manufacturing company
Horticulture practices			
AgriPhage ™ [17]	Directly targets the bacterial pathogen present on crop.	*Xanthomonas campestris pv. vesicatoria* & *Pseudomonas syringae pv* (mainly infects tomato)	Omnilytics
Food Industry			
LISTEX™ P100 [18]	To control bacterial contamination	*Listeria monocytogenes*	EBI Food Safety
EcoShield™ [19]	Do	E-coli 0157:H7	Intralytix
ListShield™ [20]	Do	*Listeria monocytogenes*	Intralytix
Veterinary practices			
BioTector [21]	As animal feed to control infections in poultry	Salmonella	Cheiljedang Corporation
Aqua Culture			
Bafador [22]	A highly efficient, stable and sustainable feed additive. It is a cocktail, comprising of five different bacteriophages, targeting bacterial pathogens in the fish's gut microbiome, for maintaining the beneficial balance	*Aeromonas* and *Pseudomonas spp.*	Proteon Pharmaceuticals
Health care setting			
FAST plaqueTB™ [23]	Diagnostic kit to rapidly identify TB disease from sputum samples	*M. tuberculosis*	Biotech Laboratories/Lab21
MicroPhage MRSA/MSSA test [24]	Diagnostic kit for identifying Methicillin resistant *S.aureus* from samples	*Staphylococcus aureus*	MicroPhage
FAST plaque-Response ™ [25]	Diagnostic kit to rapidly identify rifampicin resistant strains from positive sputum sample	*M. tuberculosis*	Biotech Laboratories/Lab21

creation of the phage library would pave the way for large scale licensing of clinical trials for a wide variety of infections, by employing these phages. These can also find application in allied areas like agriculture, where it can prove to be an effective alternative to chlorine spray, commonly used in potato farms [26].

Approximately, thousands of patients have acquired phage treatment from the above-mentioned institute [27]. For safe and centralized system of phage bank operations, it is necessary to develop standard management system through Regulatory bodies e.g. International Organization of standardization (ISO), The International Society for Biological and Environmental Repositories (ISBER) and Minimum Information about Biobank Data Sharing (MIABIS) [28].

Box 1. Checklist of Experimental Phage Therapy

Pre-requisitions

- Isolated phage should be lytic.
- It is able to demonstrate host specific as well broad spectrum of activity.
- Phage lysate must be purified appropriately.
- Phage combinations should be optimized.
- During phage production, bacterial exposure should be avoided.
- Isolated phages should be tested under certain survival factors like resistance, their genetic analysis to identify presence of virulence or mutant genes, and evaluate their level of ability to retain maximum pathogenicity, etc. [29].

In vitro experiments

- Phage purification should be carried out through filter.
- Phage titre should be determined [30].

In vivo experiments– Animal Model

- Highly purified phage is desirable.
- For topical application, only filtered phage is adequate.
- Determine in vivo phage toxicity testing.
- Various route of administration should be evaluated to measure their spectrum of activity [31].
- Bacterial identification and their load should be evaluated pre and post phage therapy.
- In absence of host, phage persistency should be monitored [12].

Regulations for phage therapy

A long while back, erstwhile Soviet Union originally had demonstrated phage therapy and was also one of the first nations to conduct clinical trials involving phages, in the 1920s. But unfortunately since then and till date, 'Phage Therapy' has mostly been limited to 'Compassionate Use' only, being employed either when the requirement is critical or when all other treatments have failed. Presently, it has find application in the treatment of various Drug-resistant bacterial infections, where antibiotics fail to show any effect. Still, regulatory authorities' e.g. USFDA has agreed on very limited number of controlled clinical trials to demonstrate the efficacy of phage therapy. So, these kind of limitations have indeed made phage therapy a 'Compassionate and Salvage Therapy Modality', till enough clinical evidences are available in its favour in the future [32]. Phage researchers working towards sustainable phage therapy should primarily focus on developing reference guidelines towards it, especially for phage formulations etc. so that it can be used in a standard way for *in vivo and in vitro* studies, till 'Phage therapy' is not approved worldwide as a realistic measure (Box 1).

Conclusion

The potential of Bacteriophages is enormous and continuously expanding, both as isolated use and also in combination with other antimicrobials especially antibiotics, to ameliorate different types of antibiotic and multi-drug resistant bacterial infections in the future. This could prove as a really significant and game-changing 'resource' in the future to curb the rising fangs of AMR, presently lurking in almost every corner of the world. Though the optimum realization of this in the future needs addressing some critical issues towards its full-scale application, like overcoming the regulatory and other bottlenecks. The findings showcased in this letter, are fully consistent with all the latest reports of various *in vitro and in vivo* studies, available in the literature.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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