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Article Review: Phage Therapy is a Potential Alternative for Antimicrobial Agents

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A B S T R A C T

As a consequence of the rapid increase in the multiple drug-resistant bacteria worldwide, an alternative strategy is urgently required. Bacteriophage as a promising approach is used for the treatment of bacterial infections. Both *in vitro* and *in vivo* studies are performed for that purpose, there is a growing evidence on the affectivity of bacteriophage to treat infections caused by gram-positive and negative bacteria. It's killing mechanism differs from antimicrobial agents by rabidly infecting the specific bacterial cell and lysing it without harming the host cell. This review focuses on the use of bacteriophage for the treatment of bacterial infections, especially multidrug-resistant bacteria.

1. INTRODUCTION

Microbials resistance to antibiotics is known as a main worldwide and expanding healthiness issue. This is reported by WHO as a future hazard of the post antimicrobial time, in which straight forward infections could be life threaten[1]. In 1915, phages were discovered and later on is known as viruses that infect bacteria. yet to a great extent disregarded in the West with the start and mass manufacturing of antimicrobial agents during the 1920s [2]. Some phage infections create methods for exploiting bacterial hosts and making more duplicates of themselves. Bacteria react with novel approaches in order to shielding themselves from viral infections. Other phages accidentally advantage microorganisms through giving genes that present resistance to antimicrobial agents, or protection from other phage viruses. For instance, at times 'mild' phage can coordinate their genes into the bacterial chromosomes which shield bacteria from other viral infections, or antimicrobial agents that usually causes bacterial destruction [3].Bacteriophages or its constructed produces can use as replacements for antimicrobial agents [4].

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As it can survive at different conditions alongside with recipient existence and has significant importance in numerous biotic procedures, as bacteriophages are the most common microorganisms on the earth [5]. It can reproduce at the infected area, which leads to bacterial lyses, yet antimicrobial agents travel through all the body and don't assemble at the infected location.

Bacteriophage application doesn't show any side effect. Whereas a bacterial resistance and allergy (in some cases a deadly anaphylactic reaction); as well as a secondary infection is frequently reported as a side effects for antimicrobial treatment [6]. Currently, Phage scientists perceive that phage life cycles can be classified into lytic and lysogenic with pseudolysogenic, chronic, and cryptic life cycle [7]. In lytic cycle the phage attached to the bacterial cell surface, infuses its DNA or RNA, reproduces through controlling the bacterial replication mechanism. This followed by host cell lysis then bursting and releasing its new progeny [8]. In 2019, the United States of FDA approved the first US clinical trial for venous phage treatment. Antimicrobial agents do not satisfy the worldwide revolution. This is due to losing the viability of antimicrobial treatment in health care could be calamitous, and are rapidly oncoming for example emergency named as "postantibiotic era" [9]. It is define as an administration of destructive phage to the infected patient by bacterial pathogen which is causes a clinically applicable infection, leads to bacterial lysis [10].

So that phage treatment can be a successful option in contrast to antimicrobial agents, that can likewise aggravate bacterial infections by expanding protection from antimicrobial agents on the off chance that they are not properly chosen and harvested [11], alteration between the competitor bacterial species [12], and mediate the replace of genetic material among bacteria by the use of HGT [13]. Microorganisms are continually advancing to avoid phage infections and phages are gaining new ways to taint their bacterial hosts [14,15] .To elaborate the population dynamics of phage-bacteria interactions, both experimental and theoretical studies have been undertaken.

2. BACTERIOPHAGE BIOLOGY

Bacteriophages are known as a group of obligate intracellular parasites that infects bacteria in a specific manner and can be easily manipulated. They can be found in all environments as long as their host are existed [5,16]. Its genome is a ss/ds DNA or RNA. The majority of the identified phages are classified under the order Caudovirales (dsDNA with tailed morphology) which includes three families, *Siphoviridae*, *Myoviridae* and *Podoviridae* [17]. Based on its life cycle, bacteriophages are either lytic (virulent) or lysogenic (temperate). The lytic phage is attached to the cells' host surface and the phage genome is injected in to the host cytoplasm. With the use of bacterial molecular machinery, virions are produced and released through destroying the host cell. Two proteins (Holin and lysin) are used for that purpose. In which holin is a membrane protein, which oligomerized to produce channels into the plasma membrane providing a route for lysine release. While lysin cleaves bonds in the bacterial cell wall peptidoglycan to release new phages progeny [18,19]. The cycle is repeated as long as host bacteria are present [8,20]. On other hand, the lysogenic cycle differs from the lytic cycle by integrating their genome with host nucleic acid and becoming as a prophage. This process allows viral replication within the host cell genome and under specific stimuli, the prophage in the dormant stage will burst into lytic cycle [21,22]. The lysogenic cycle allows horizontal gene transfer such as antibiotics resistant genes or virulence factors. For that reason, lysogenic phages are not used for phages therapy [23]. A third type of life cycle was detected in filamentous phages in which host cell is killed by the bacteriophages without bacterial genome lysis [24].

3. BACTERIOPHAGE SAFETY

The exploit of phages as a unique therapeutic agent which provides for a person infected with bacteria is known as classical phage therapy. In which a single bacteriophage or a mixture of two bacteriophages is utilized for that purpose [25]. Bacteriophages are conservationists and depend on environmental choice, separating and recognizing microbes. This is a rapid procedure in comparison with the novel antimicrobial agents' improvement, that takes numerous durations, extremely expensive, and ineffectual [26]. For sustainable bacteriophage treatment, itis necessary to convey to the infected region with a sustainable therapeutics level during an adequate time. This treatment can be intake enteral, topical, inhaled or infused a long shot with the most well-known [27]. As it is attached to the bacterial cell then infuse its genome into the cell. After that, its genome adequately replaces the bacterial genome, stopping bacterial cell replication. Bacteriophages are extremely precise up to bacterial strains. This therapy has several advantages a decrease in the side effects and the danger of development in bacterial resistance.

On other hand, there is trouble in finding of an effective phage for the specific infection [28]. Hypersensitivity is most unfavorable reaction correlated to certain types of antimicrobial agents or elevation into mass concentrations [29]. As opposed to the complete literature on antimicrobial safety, phage treatment has late support from western medication so that the significant data of bacteriophage security is totally novel. While mouth bacteriophage intake is commonly measured as a safe route [30].

The possibility of bacteriophage treatment to disturbance typical intestine barrier capabilities could has a real ramification such as Crohn's disease, inflammatory bowel disease, and type 1 diabetes [31]. Phage therapy has a number of advantages in comparison to traditional antibiotic therapy. Phage separation is rapid, straightforward, and inexpensive. Bacteriophage renitence takes long time to develops and slower than antimicrobial resistances [32]. Stability of its virulence under extremely brutal ecological conditions and will in general last duplicating until the bacterial population density be decreased [33]. Despite the fact that bacteriophage therapy is used for several span to different infections, few countries used it as a counter strain in practical medication. Meanwhile, security is the first primary worries while considering the use of bacteriophages as a cure or prophylaxis, in contrast to normal pharmacological items, it is alive creature. Moreover, it may be supply to horizontal gene transfer as transduction [34].

Genomic properties of phages are significant in order to foretell its "security" in therapy uses as exhibited through a few specialists. Bacteriophages can used as a carriers for HGF in bacteria, once it's being engaged with virulent trade or antimicrobial resistant gene constructing a pathogenically progressive bacteria or impervious antimicrobial agent [35]. Various clinical preliminaries have shown that phages safety and lytic enzymes are in concurrence with the examinations into the animal models or as detailed in various readings. While, several phases one and additionally phase two medical preliminaries to show the effectivity of bacteriophages in contradiction of ESKAPE diseases have been enlisted in the previous scarcely any years, the quantity

of all-around recorded and finished preliminaries are very low to even consider drawing significant conclusions [36].

4. BACTERIOPHAGE THERAPY TO BACTERIAL INFECTION

The reintroducing of phage therapy as a promising choice to treats and /or prevent infections with multidrug-resistant bacteria is growing in the recent years. The concept known, as phage therapy is not new in the science field and brought back with the emergence of multidrug-resistant bacteria [37]. In which it exterminates bacterial cells in different modes that the mechanisms of used antimicrobial agents. When the phage enter their specific host they multiply rapidly and causes lysis of the bacterial cell to release their progenies as a result to this process the host cause reduced [38]. This therapy exhibits numerous advantages in comparison to antibiotics therapy. The pathogens and normal flora of patients are the targets of antibiotics while bacteriophage infect their bacterial hosts specifically [6,26]. This therapy is also used for controlling bacterial plant diseases or as a pest agent. A phage cocktails of *Podoviridae* phage's had the ability to suppress *Pectobacterium* growth both *in-vitro* and *in-vivo* which causes soft rot blackleg of potato resulting in economic losses in vegetable industry [39]. By using random amplification of polymorphic DNA (RAPD) PCR, transmission electron microscopy and coevolution experiment, phage's cocktails belong to both Myoviridae and Podoviridae families.

This cocktail can reduce the Bleeding canker of horse chestnut trees disease caused by *Pseudomonas syringae pv. aesculi* [40]. Another in vitro study indicated that two phages were isolated from plantations of Colombia inhabited the growth of *Ralstonia* solanacearum, which is the causative agent of Moko disease in banana and plantain [41]. An industry study indicated that a phage belong to the family Podoviridae (isolated form sludge) had a lytic activity against Pseudomonas lactis strain in milk and the phage was still active during cold storage at 3°C [42]. There is encouraging results were reported from the use of Phage cocktails in the animal's models and few clinical studies [43]. Recently, three Myoviridae bacteriophages were intravenously administered to 13 patients in an Australian hospital suffering from severe Staph. aureus infections. Its results shows that bacteriophage cockatiels were safe with no evidence of adverse reactions [44]. However, more trials are needed to determine effectiveness of the phage cockatiels.

5. CONCLUSIONS

Phage therapy as a developed drug for treating multidrug-resistant bacteria is very important due to the rapid expansion of that bacteria. It is advisable to use it due to the survival of Bacteriophages in different conditions as long as their host are existing without any side effects in comparison to antimicrobial agents. While the antimicrobial treatment includes several side effects such as bacterial resistant, and secondary infections. Phage therapy includes using a combination two or more phages depending on natural selection, isolating and identifying bacteria. It is also used for controlling bacterial plant diseases or as a pest agent. Further studies are necessary to validate these results and test them on more animals' models.

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العاثيات العلاجية كبديل محتمل للعلاج بعوامل المضادات الماكروبية

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الخلاصة:

نتيجة للزيادة السريعة في ظهور أنواع بكتيرية مقاومة للعديد من الادوية في مختلف أنحاء العالم، مما اوجب ذلك الى ايجاد استراتيجية بديلة لهذا الغرض. يعتبر استخدام العاثيات البكتيرية كنهج واعد لعلاج الالتهابات البكتيرية. حيث تم إجراء كل من الدراسات في المختبر وفي الجسم الحي لهذا الغرض، وهناك أدلة متزايدة على فعالية استخدام العاثيات البكتيرية في علاج الالتهابات التي تسببها البكتيريا موجبة والسالبة لصبغة كرام. اذ تختلف آلية القتل فيها عن استخدام المضادة للميكروبات من خلال إصابة الخلية البكتيرية المعينة بفترة قصيرة من ثم تحليلها دون الإضرار بالخلية المضيفة. تركز هذه المراجعة على استخدام العاثيات البكتيرية كعلاج للالتهابات البكتيرية، وخاصة البكتيريا التي تمتاز بصفة المقاومة للعديد من الأدوية.