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Original Paper

Bacteriophage therapy as an alternative approach: The future of phage-based treatments in combating antibiotic resistance

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ABSTRACT

The rapid rise of antimicrobial resistance has weakened the clinical value of many antibiotics and complicated the management of burn wound infections. This study investigated bacterial pathogens recovered from burn wounds in Ramadi City and evaluated wastewater-derived bacteriophages as a targeted option against drug-resistant isolates. A total of 100 burn wound swabs were collected from patients (12-65 years) at Ramadi City Hospital between September 15, 2024, and January 17, 2025. Isolates were cultured on selective media, identified by microscopy and biochemical testing, and confirmed using the VITEK_2 Compact system. Antimicrobial susceptibility was assessed by the Kirby–Bauer disk diffusion method using 12 antibiotic disks interpreted according to CLSI 2024. Biofilm production was screened, and molecular confirmation was performed using conventional PCR targeting the 16S rRNA gene with electrophoretic visualization and sequencing for verification. Environmental wastewater samples from a local wastewater filling station were used for phage enrichment, isolation by the double agar layer method, plaque purification, and morphological characterization by transmission electron microscopy (TEM).

Eighty-six bacterial isolates were obtained from the 100 samples; 14 samples showed no growth. *Staphylococcus aureus* was the predominant organism (54%), followed by *Pseudomonas aeruginosa* (9%), *Klebsiella pneumoniae* (7%), *Escherichia coli* (5%), *Enterobacter aerogenes* (4%), and *Serratia marcescens* (3%), with several species detected as single isolates. Lytic bacteriophages were recovered only against *S. aureus*; no lytic activity was observed against *E. coli, P. aeruginosa,* or *K. pneumoniae* under the conditions tested. TEM revealed tailed phage particles consistent with common staphylococcal bacteriophages. Overall, wastewater-derived phages showed strong host specificity for *S. aureus*, supporting further work to optimize isolation conditions, expand host-range screening, and evaluate combined phage-antibiotic strategies for burn wound infections.

Keywords: *Bacteriophage, Lytic phage, Plaques distributed, TEM microscope*

1 INTRODUCTION

One of the biggest threats to world health in the twenty-first century is bacterial resistance to antibiotics. Antibiotic overuse and misuse have led to the evolution of resistant bacterial strains, which raise mortality and persistent infections while undermining the efficacy of traditional treatments [1]. The use of plant and natural extracts, such as garlic, honey, ginger, thyme, and cinnamon, has been proven effective in fighting bacteria, boosting the immune system, and reducing the side effects associated with traditional antibiotics [2]. With their novel and potent mechanisms of action, nanoparticles offer a potential alternative to traditional antibiotics in the fight against resistant microorganisms [3]. These technologies can selectively penetrate and destroy bacterial membranes

due to their unique physical and chemical properties. Since silver nanoparticles (AgNPs) have broad-spectrum antibacterial activity, they are among the most commonly used. They cause oxidative stress by generating reactive oxygen species (ROS), destroying DNA, and changing the permeability of the bacterial cell membrane. Additional instances include nano-selenium, nano-zinc oxide, nano-gold, and nano-titanium dioxide (TiO_2) (1).

Because of its unique properties, bacteriophage therapy has become a viable alternative in this situation. The ability of bacteriophages to infect specific bacterial species without harming beneficial bacteria or human cells reduces the risks associated with the common adverse effects of antibiotic use [4]. They can also break through biofilms and eliminate them, which often reduce the effectiveness of antibiotics. Target bacteria are less likely to become permanently resistant to treatment when bacteriophages can evolve alongside them [5]. Bacteriophage therapy has been shown in clinical and case studies to be beneficial for treating pneumonia, wound infections, and cystic fibrosis, even when antibiotics have failed completely. Some bacteriophage "cocktails" are currently on the market, while others have been created to target a wider range of bacteria or to fight multi-resistant types [6]. By genetically modifying bacteriophages and broadening their target range, as well as by combining them with antibiotics to achieve synergistic effects, efforts are being made to increase the effectiveness of treatment [7]. With the creation of appropriate regulatory frameworks and the growing acceptance of this treatment by medical and public communities, bacteriophage therapy is anticipated to serve as an adjunct or even a substitute for antibiotics in the treatment of drug-resistant bacterial infections [8].

This study assesses the effectiveness of bacteriophages in eradicating antibiotic-resistant bacteria, focusing on their ability to specifically target certain bacterial strains while preserving beneficial bacteria.

2 MATERIALS AND METHODS

2.1 Bacterial strains

E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter aerogenes, Serratia marcescens, and *Klebsiella pneumoniae* isolates were isolated and identified in this study.

2.2 Study samples

Bacterial samples were collected. For this investigation, 100 samples were collected from patients with burn wound infections. Swabs were taken from 100 patients, both sexes aged 12–65 years, with acute infections. The collection period for the pathology samples was September 15, 2024, to January 17, 2025. A swab from the affected area was taken using sterile cotton swabs. After that, the samples were cultivated on culture media (MacConkey, Mueller Agar, Mannitol, Nutrient, and Blood Medium) and characterized. The bacteria were initially diagnosed morphologically by microscopy, then biochemically, followed by the VITEK_2 Compact system. Susceptibility tests were performed using the disk diffusion method to identify the most antibiotic-resistant strains [9]. Twelve antibiotic disks were used as indicated in Table 1 (Liofilchem, Italy) and tested for efficacy against *E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter aerogenes, Serratia marcescens,* and *Klebsiella pneumoniae,* using the Kirby–Bauer disk diffusion method [10]. The inhibition zone diameters were measured and compared with those reported in CLSI 2024 [11].

Biofilm testing was then performed to identify highly productive, intermediate, and weak biofilm-producing strains. Molecular diagnosis was then performed using PCR targeting the 16S rRNA gene [12]. Conventional PCR was performed to detect the presence of housekeeping genes (16S rRNA) in all *S. aureus, K. pneumoniae,* and *P. aeruginosa isolates.* The PCR product was detected by electrophoresis [12], followed by sequencing for confirmation. Environmental samples were then collected for the isolation and identification of bacteriophages. Wastewater was used in this research; it was taken from a wastewater filling station, transported to the laboratory in sealed, opaque containers, and stored at 4 °C until use. Bacteriophage application was performed against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella pneumoniae*. The most resistant and most sensitive isolates were selected after performing sensitivity testing for each species.

2.3 Host bacterial culture preparation

2.3.1 Bacterial growth

To reach the exponential growth phase (OD600 = 0.6), the target bacterial strain (e.g., *Escherichia coli, Staphylococcus aureus*) was activated in a liquid medium and incubated at 37 °C for 18-24 h.

2.3.2 Purity confirmation

The culture was grown on nutrient agar plates and examined for contamination using Gram staining.

2.4 Bacteriophage isolation

Steps for enrichment: Ten milliliters of the active host bacterial culture were combined with 10 mL of the environmental sample.

Lower-layer preparation: LB agar (1.5% agar) was added to Petri plates and allowed to solidify.

Table 1 Antibiotic discs used in the study

No.	Antibiotic (Symbol - concentration)	Manufacture (Origin)
1	Erythromycin (ER-15 μg)	Bioanalyse (Turkey)
2	Clindamycin(CL-2 μg)	Bioanalyse (Turkey)
3	Ceftriaxone (CTF - 10μ g)	Bioanalyse (Turkey)
4	Lavofloxacin (LEV −5μ g)	Bioanalyse (Turkey)
5	Gentamycin (GEN - 10μ g)	Bioanalyse (Turkey)
6	Cefixime (CM-5 15μ g)	Bioanalyse (Turkey)
7	Meropenem (MRP - 10μ g)	Bioanalyse (Turkey)
8	Methicillin (MET - 10μ g)	Bioanalyse (Turkey)
9	Aztreonam (AZ-30 15μ g)	Bioanalyse (Turkey)
10	Piperacillin (PIT - 100μ g)	Bioanalyse (Turkey)
11	Cefepime (CEP-30 15μ g)	Bioanalyse (Turkey)
12	Tetracycline (TE −10μ g)	Bioanalyse (Turkey)

2.5 Topmost layer

The host bacterial culture (100 µL) was combined with 100 µL of the filtered filtrate. This step was accompanied by a series of dilutions by adding 50 µL of SM buffer for bacteriophages (SM buffer: 1 M Tris-HCl, pH 7.5; 5.8 g NaCl; 2 g $MgSO_4.6H_2O$ in 1 L distilled water). The goal of dilution was to reach the required bacterial density so that the phage could infect the bacteria, because density plays an important role and has a strong impact on phage effectiveness at high density. The mixture was poured over the lower layer after it was added to 3 mL of soft agar (0.7% agar). The plates were incubated at 37 °C for 18-24 h.

Plaque monitoring: The plates were checked for bacteriophage-induced lysis patches (plaques). Then, the phage was collected using a wooden stick or tips, placed in dimethyl sulfoxide (DMSO) buffer, stored at -80 °C, and sent for examination by transmission electron microscopy (TEM).

3 RESULTS

3.1 Identification of bacteria

Eighty-six bacterial isolates were studied from 100 samples taken from burn wound patients in Ramadi City. *Staphylococcus* aureus was the most common pathogen (54%), followed by *Pseudomonas aeruginosa* (9%). Enterobacter species, led by *Klebsiella pneumoniae* (7%), were also identified, along with *Escherichia coli* (5%), *Enterobacter aerogenes* (4%), and *Serratia marcescens* (3%). *Staphylococcus haemolyticus, Enterococcus faecalis, Enterobacter cloacae* complex, *Serratia odorifera,* and *Klebsiella oxytoca* were each detected as single isolates (Table 2). Fourteen of the 100 samples showed no growth.

Table 2 Bacterial species isolated and identified in the current study

Bacteria	numbers
Staphylococcus aureus	52
Staphylococcus haemolyticus	2
Pseudomonas aeruginosa	8
Enter ococcus faecalis	1
Enterobacter cloacae complex	1
Enterobacter aerogenes	4
Serratia marcescens	3
Serratia odorifera	1
E coli	5
Klebsiella pneumoniae	7
Klebsiella oxytoca	1
Total number	**86**

Each isolate was then examined microscopically to determine morphology, aggregation pattern, and Gram staining response (Figure 1). Then, biochemical tests were performed, including the IMVC test for the Enterobacteriaceae family, which yielded positive results for each species. The VITEK_2 Compact system was then used to identify both Gram-negative and Gram-positive isolates. The VITEK-2 compact system allows automated diagnosis supported by an extensive database of biochemical tests (BioMérieux).

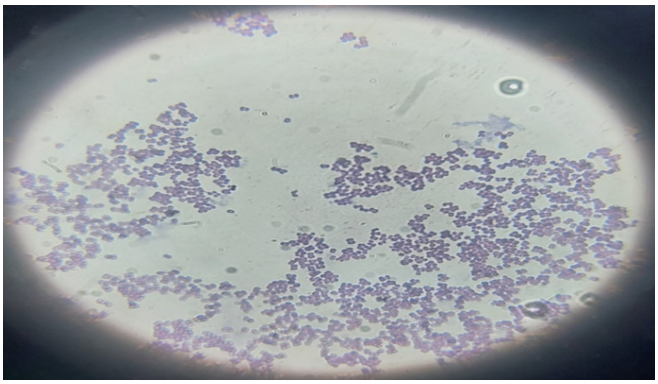

Fig. 1 Microscopic examination of *S. aureus* isolates

3.2 Molecular detection

The results of PCR products using gel electrophoresis showed 179 bp for *S. aureus* 16S rRNA, on the right of the image, and 198 bp for *P. aeruginosa* on the left of the image (Figure 2A), and 16S rRNA for *K. pneumoniae* (Figure 2B). The gel was run with 1.5% agarose, 1X TAE, and at 70 volts for 55 min.

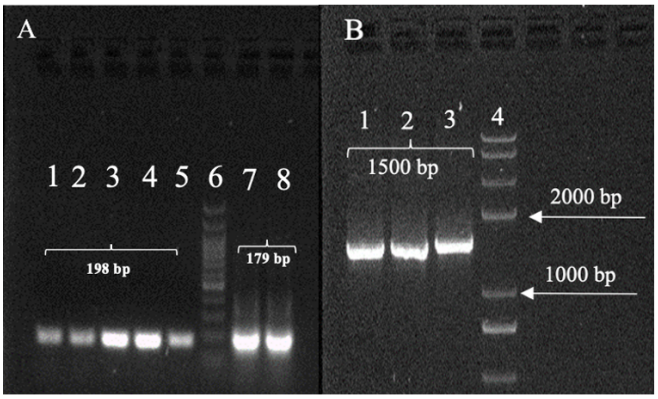

Fig. 2 Gel electrophoresis of 16S rRNA PCR product for isolated bacteria. (A) Lane 1-5: PCR product (179 bp) for *S. aureus* bacteria (the right of the figure), Lane 6: 100 bp ladder, Lane 7-8: PCR product (198bp) for *P. aeruginosa* (the left of the figure), (B) Lane 1-3: PCR product (1500 bp) for *K. pneumoniae*, Lane 4: Trans 2k plus II DNA ladder, with 1.5% agarose, 1X TAE, and at 70 volts for 55 min

3.3 Bacteriophage plaques

Figure 3 shows an agar plate containing LB agar with *Staphylococcus aureus* growing and numerous clear plaques distributed across the surface. These plaques represent areas of bacterial lysis resulting from lytic bacteriophage activity. Figure 4 shows a double-layer agar plate containing an antibiotic-sensitive *Staphylococcus aureus* colony, with clear areas (plaques) indicating phage-mediated lysis of the bacterial cells.

3.4 Transmission electron microscopy

Figure 5 represents the results of a transmission electron microscopy (TEM) examination of bacteriophages that infected *Staphylococcus aureus* at 10,000x magnification and at a resolution of 500 nanometers. It shows a number of viral particles (phages) with the sizes and shapes characteristic of phages specialized in targeting *S. aureus*. Figure 6 indicates a size of 200 nm and a very high magnification (27,800×). It displays bacteriophage particles with prominent tails and icosahedral heads. Figure 7 shows a high-magnification image at 100,000x with a resolution of up to 30 nm.

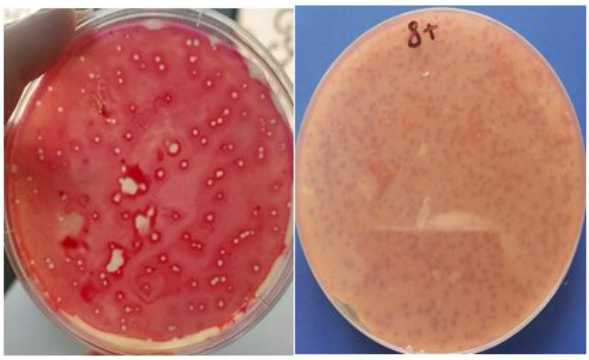

Fig. 3 Plaque assay of high lytic activity of isolated phage against clinical isolate of *S. aureus*

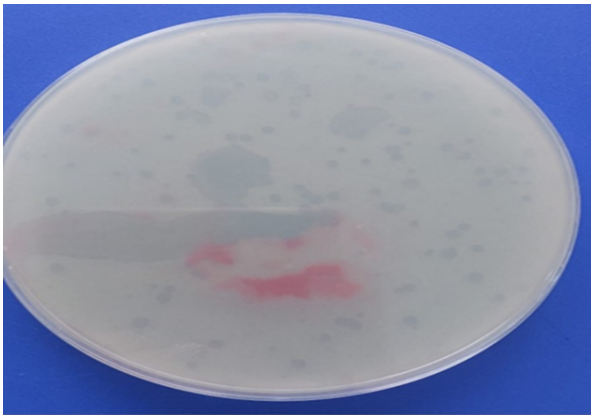

Fig. 4 The double-layer agar (DLA) method for isolation and purification of *S. aureus* bacteriophages

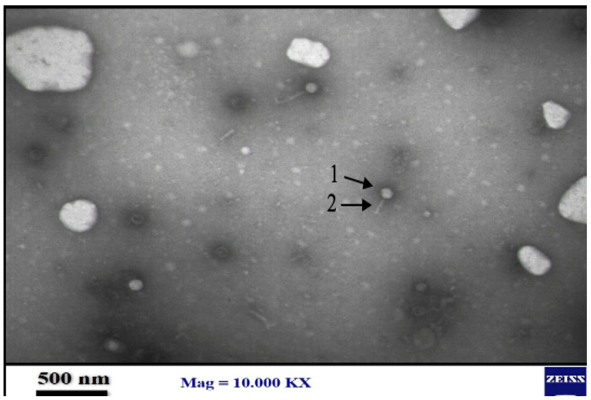

Fig. 5 TEM examination of *S. aureus* bacteriophages. It shows number of viral particles (phages), 1- black arrow: phage head and 2- black arrow: phage tail, 10,000x magnification and resolution of 500 nm

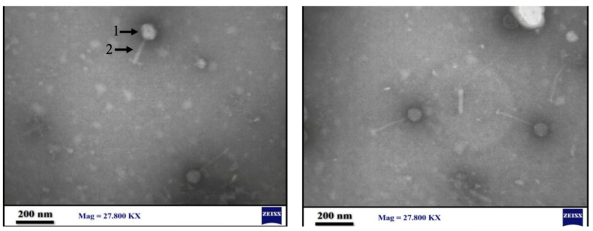

Fig. 6 TEM examination of *S. aureus* bacteriophages. It shows number of viral particles (phages), 1- black arrow: phage head and 2- black arrow: phage tail, 27,800x magnification and resolution of 200 nm

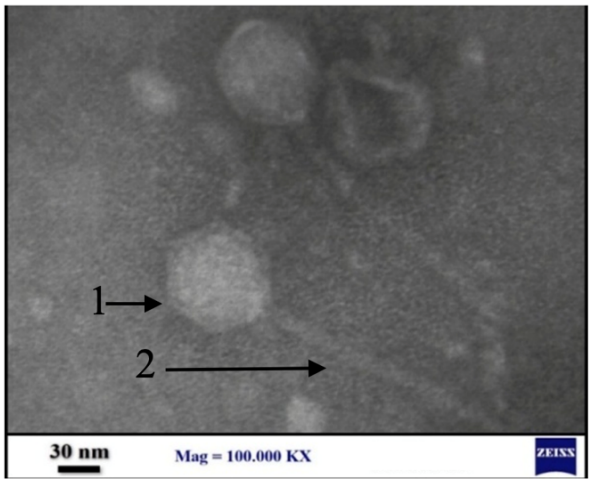

Fig. 7 TEM examination of *S. aureus* bacteriophages. It shows number of viral particles (phages), 1- black arrow: phage head and 2- black arrow: phage tail, 100,000x magnification and resolution of 30 nm

4 DISCUSSION

This study assessed the prevalence of burn injuries and the resistant bacteria linked to burn of patients in Ramadi City. From 100 samples collected from burn patients, 86 bacterial isolates were examined. *Pseudomonas aeruginosa* (9%), *Klebsiella pneumoniae* (7%), *Escherichia coli* (5%), *Enterobacter aerogenes* (4%), and *Serratia marcescens* (3%). *Staphylococcus aureus* (54%) was the most prevalent pathogen. The only (single) isolates were S*taphylococcus haemolyticus, Enterococcus faecalis, Enterobacter cloacae, Serratia odorifera,* and *Klebsiella oxytoca.* These findings support the medical literature's assertion that *S. aureus* is a common cause of infection, particularly in clinical samples related to wounds and pus [13].

Conventional PCR was used to detect the presence of the housekeeping gene (16S rRNA) in all *S. aureus*, *K. pneumoniae*, and *P. aeruginosa* isolates. The PCR product was detected by electrophoresis. Amplification of the 16S rRNA gene is among the most common molecular methods used to study bacterial phylogeny [14]. There were many reasons for choosing this gene as a diagnostic marker, including its presence in almost all bacteria, a conserved region with a stable function, its size, which provides sufficient information, and its occurrence as an operon or multigene family. Many researchers have shown that this gene is an ideal tool for diagnosing *S. aureus* [15]. Faeq Ahmed and Abbas Hatite Al-Daraghi [14] reported that molecular detection of 16S rRNA and 23S rRNA provides accurate tools for diagnosing *S. aureus*, with complete (100%) distribution among the study isolates. After the bacterial isolates were identified, they were treated with bacteriophages to isolate and identify viral phages and analyze the pathogenic bacteria.

As they bind to specific regions on bacterial surfaces, bacteriophages are typically very selective and exclusively target particular kinds of bacteria. The bacteriophage recognizes distinct surface receptors on the host bacterial cell wall, such as *S. aureus* proteins [16, 17]. Adaptations to the environment can change over time. Phage species specific to common pathogens, such as *S. aureus* (which is linked to skin and human illnesses), arise in contaminated settings such as sewage [18]. A high density of *S. aureus* in a wastewater sample increases the likelihood of specialized phage proliferation, in addition to the concentration of host bacteria. Environmental pressure: phages that target resistant bacteria, such as methicillin-

resistant *Staphylococcus aureus* (MRSA), may evolve in settings with high antibiotic exposure, such as hospitals. Isolation technique: phage growth compatible with *S. aureus* is favored when it is used as the sole host during amplification [17].

A double-layer agar plate with *Staphylococcus aureus* resistant to eight different antibiotic types had many transparent plaques on the medium's surface. The efficacy of lytic phages against this multidrug-resistant strain is demonstrated directly by these transparent plaques, which show regions of *S. aureus* cells lysed by bacteriophages. Plaques of this density and frequency indicate that the isolated phages can successfully infect and lyse *S. aureus* cells that are resistant to antibiotics. Each plaque represents a cycle of phage replication in which the phage binds to the bacterial cell, inserts its genetic material, and ultimately causes cell lysis and the release of new phages to target nearby cells [19, 20].

Research shows that, even when antibiotics are ineffective, phages that lyse *S. aureus* can eradicate resistant bacteria. This is because their mode of action, which targets the cell wall and directly degrades it, is entirely distinct from that of antibiotics. Phage therapy has also been shown to dramatically lower bacterial burdens and improve cure rates in both human and animal experiments [21].

Research indicates that *S. aureus* that is resistant to antibiotics is not always resistant to phages, and vice versa. Phages are a versatile and efficient treatment option for a variety of illnesses because they can target and eliminate both susceptible and resistant bacteria [21].

Research shows that phages and antibiotics can work together to reduce bacterial loads and prevent the emergence of resistance in both susceptible and resistant strains. In addition, some research has shown that using phages in conjunction with, or before, antibiotics improves treatment efficacy and lowers the risk of developing new resistance [22].

The remarkable effectiveness of lytic phages against *S. aureus* is demonstrated by the agar plate findings. The transparent patches indicate that the phages completed a full life cycle, infecting and lysing bacterial cells and leaving areas devoid of bacterial growth. Significance of clear spots: The phage's ability to infect and lyse staphylococcal cells is indicated by the large number of clear spots of varying sizes. The size and concentration of the spots are directly influenced by the phage type and the viral particle concentration (MOI) used [23].

High phage quality: the spots that appear consistently and clearly suggest that the preparation used was of high quality for the tested staphylococcal strain. This is crucial for phage therapy applications, particularly when dealing with antibiotic-resistant bacteria. These findings are consistent with earlier research showing that phages isolated against *S. aureus* can produce discrete spots on growing media. Depending on the phage type and experimental setup, these spots are often round or oval and range in size from 1.5-2.6 mm [24].

Spot size variation: To determine the optimal conditions for maximal bacterial lysis, further research is needed. Spot size variation may indicate phage mutations or differences in bacterial density. The phage was then identified by transmission electron microscopy.

TEM results showed a number of viral particles (phages) with sizes and shapes characteristic of phages specialized in targeting *S. aureus*. The image shows small particles with noticeable tails and shaped heads, which are the main features of phages from the Siphoviridae and Myoviridae families that often infect *S. aureus* [25]. While tail length varies based on the phage species and can be long and flexible (as in Siphoviridae) or flexible and contractile (as in Myoviridae), head diameter usually falls between 80 and 110 nm [26]. The image clearly displays bacteriophage particles with a prominent tail and an icosahedral head, which are typical structural characteristics of phages belonging to the Caudovirales order, especially the Siphoviridae or Myoviridae families, which are shared by many *S. aureus* phages [27]. In line with descriptions of Siphoviridae, which typically have heads 40–80 nm in diameter and long, non-contractile tails, or Myoviridae, which have larger, contractile tails, the image depicts a phage particle with an icosahedral (many-faceted) head and a comparatively long tail [26].

Icosahedral head structures, the most common structural form among phages, with the ability to distinguish subtle structural details [28]. The best-known bacteriolytic phages, such as T4 and P1, belong to the order Caudovirales, which is characterized by a complex viral head structure. The presence of this structural pattern validates the type of sample under study and supports phage classification within recognized families [29].

The pictures are quite good at showing the phage's structural features, such as the edges of the viral head and, occasionally, a portion of the tail. According to recent research, the transmission electron microscope (TEM) is one of the best instruments for phage classification because it allows differentiation of viral families according to head, tail, and tail fiber shapes, a crucial

criterion in contemporary viral classification [30]. These findings align with current research on the value of TEM in phage characterization. This method has been used to identify over 5,500 phage species, making it a vital tool for quick virus diagnosis and categorization. Research has also shown that effective phage identification depends on maintaining structural characteristics, such as the borders of the viral head and tail segments, as seen in the accompanying figures [30].

5 CONCLUSION

From 100 burn-wound swabs collected in Ramadi City, 86 bacterial isolates were recovered, with *Staphylococcus aureus* as the dominant pathogen, followed by Pseudomonas aeruginosa and Enterobacteriaceae, including *Klebsiella pneumoniae* and *E. coli*. Identification was supported by culture/biochemical testing, VITEK_2, and 16S rRNA PCR. Wastewater screening yielded lytic bacteriophages against *S. aureus* only, producing clear plaques and showing tailed phage morphology by TEM, whereas no lytic activity was detected against the other tested species under the same conditions. These findings highlight burn wounds as an important reservoir of resistant bacteria and indicate that locally sourced, highly specific anti-*Staphylococcus* phages could be a practical supportive option, but broader sampling and optimized isolation/host-range testing are needed before considering wider clinical use.

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Author contributions

S.T.M. designed the study , R.T.S. conducted experiments, R.T.S. wrote the manuscript

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Data availability

N/A

DECLARATIONS

Conflict of interest

The authors declare that there is no conflict of interest.

Consent to publish

N/A

Ethical approval

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