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Literature Review on the Therapeutic Potential of Bacteriophages Against Resistant *Staphylococcus aureus*

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major driver of antimicrobial resistance and necessitates precise non-antibiotic therapeutics. This review comprehensively evaluates evidence on bacteriophage therapy against resistant *S. aureus* and the molecular and structural barriers that limit efficacy. A structured search of PubMed, Scopus, Google Scholar, ScienceDirect, KAKEN, and ResearchGate identified peer-reviewed studies published up to 2025 using predefined keywords. Articles were screened and synthesized thematically across vitro assays, *Ex Vivo* burn-wound models, and host-range/biofilm studies, with mechanistic mapping of mecA/PBP2a and O-acetyltransferase A (OatA), and appraisal of dosing strategies (single, repeated, prophylactic). Findings show consistent phage-mediated reductions of *S. aureus in vitro*; in *Ex Vivo* human/porcine skin, higher doses and repeated application enhanced suppression, and prophylaxis prevented colonization. Activity against biofilm was strain- and phage-specific; some phages reduced biomass while others paradoxically increased it, and narrow host range plus OatA-linked barriers persisted. In conclusion, bacteriophages are promising but require precise strain matching and micro-environmental consideration. The research highlights the importance of biofilm-aware screening, strategic formulation of phage cocktails or lytic enzymes, optimized dosing regimens for repeated or prophylactic use, and the integration of molecular characterization with synthetic phage engineering to broaden host range and accelerate translation into clinical applications.

Keywords: Antimicrobial resistance, bacteriophage, MRSA, O-acetyltransferase A (OatA), *Staphylococcus aureus*.

Introduction

Antimicrobial resistance has become one of the most serious global health threats as identified by the WHO, with an estimated over 4.9 million associated deaths in 2019 and a projected economic loss of up to USD 100 trillion by 2050 (Habboush & Guzman, 2023; O'Neill, 2016; Prasetyaning Amukti *et al*., 2024; World Health Organization, 2017, 2022). This condition is exacerbated by inappropriate antibiotic use, including over-prescription and premature discontinuation, which can accelerate the development of bacterial resistance (Arulkumaran *et al*., 2020; Habboush & Guzman, 2023; Sukertiasih *et al*., 2021). Apart from the health impact, new antimicrobial drug development is also hampered by low economic incentives, leading many pharmaceutical companies to shut down antibiotic research divisions since 2019 (Lee Ventola, 2015; World Health Organization, 2022).

Staphylococcus aureus is an opportunistic Gram-positive bacterium that can cause various infections, ranging from skin infections to sepsis, often evolves into Methicillin-resistant Staphylococcus aureus (MRSA) (Chandra et al., 2024; Irianto, 2014; Liu et al., 2024; Nugroho et al., 2016; Salsabila et al., 2025). MRSA accounts for a high prevalence in Asia, with mortality rates

up to 40% higher than those of non-resistant infections (Mutmainnah et al., 2020; Skrupky et al., 2009; Tong et al., 2015; World Health Organization, 2022). Resistance in MRSA is primarily driven by the presence of the mecA gene encoding PBP2a, an enzyme that diminishes the efficacy of β-lactam antibiotics, as well as structural factors such as biofilm formation and cell wall modifications by O-acetyltransferase A (OatA) (Abdraimova et al., 2024; Azeredo et al., 2017; Górski et al., 2018; Jones et al., 2020; Nova et al., 2024; Oliva et al., 2021; Sanchez et al., 2017).

Although last-line antibiotics such as vancomycin and linezolid are still in use, their effectiveness is steadily declining due to ongoing resistance development and significant systemic side effects (Fair & Tor, 2014; Irianto, 2014; Skrupky et al., 2009). The challenge is compounded by multi-drug resistance, in which strains exhibit resistance to multiple antibiotic classes simultaneously (Habboush & Guzman, 2023; World Health Organization, 2022; Prestinaci et al., 2015; Talbot et al., 2006;). These factors highlight the need for alternative therapies with high precision. Bacteriophages, viruses that specifically infect bacteria, offer such an alternative and can kill bacteria rapidly through lytic cycle (Brives & Pourraz, 2020; Górski et al., 2018).

Bacteriophages offer great potential in overcoming resistant S. aureus infections, but their effectiveness can be influenced by molecular factors such as biofilm formation, peptidoglycan modification by OatA, and PBP2a expression (Brives & Pourraz, 2020; Górski et al., 2018; Widodo, 2022). Therefore, this study aims to comprehensively review the therapeutic potential of bacteriophages against resistant *S. aureus*, identify the molecular and structural barriers that affect phage effectiveness, and explore innovations in synthetic phage engineering to enhance therapeutic precision and host range in the future.

Material and Methods

This research employs a narrative-descriptive literature review approach aimed at evaluating the therapeutic potential of bacteriophages against resistant *Staphylococcus aureus*, particularly in molecular and applied contexts. The literature search was conducted through various leading scientific databases such as Google Scholar, Scopus, PubMed, KAKEN, ResearchGate, and ScienceDirect, limiting the publication period to 2015–2024 (Alifiyah, Aryanto, dan Zikriyani 2025).

Articles included in the review were selected based on their relevance to the research focus, namely phage activity against *S. aureus*, especially strains that exhibit antibiotic resistance. The keywords used in the search included: "bacteriophage", "*Staphylococcus aureus*", "MRSA", "endolysin", "holin", "OatA", and "biofilm", in both Indonesian and English.

Article searches were performed using the keywords: "bacteriophage", "*Staphylococcus aureus*", "MRSA", "endolysin", "holin", "OatA", and "biofilm". The inclusion criteria encompassed articles that directly examine bacteriophage activity against *S. aureus*, particularly strains that have demonstrated antibiotic resistance. Meanwhile, the exclusion criteria included articles that discuss bacteriophages in contexts outside clinical pathogens (such as food or environmental contamination), as well as articles that do not specifically address bacterial resistance.

All references analyzed were from online peer-reviewed journals and were highly relevant to the focus of the review. The collected literature was then analyzed thematically to evaluate phage mechanisms of action, molecular challenges such as the mecA gene and the OatA enzyme, as well as the potential of synthetic phage engineering as a precision therapeutic strategy against multidrug-resistant *S. aureus* infections.

Results and Discussion

Antibiotic Resistance Profile of *S. aureus* Isolates

Table 1 displays the resistance profile of five *S. aureus* isolates against eighteen commonly used antibiotics (Irianto, 2014; Prestinaci *et al*., 2015; Tong *et al*., 2015). From the data, it is shown that most strains are sensitive to all antibiotics, and three of the eighteen strains were resistant to several antibiotics. The isolate 1656 showed the highest MDR pattern, being resistant to nine of the eighteen antibiotics, including gentamicin, ciprofloxacin, and

oxacillin. The strain ATCC 5923 was used as a sensitive control due to its susceptibility to antibiotics and its Biofilm common use as a quality control strain (Treangen et al., 2014).

Table 1. Antibiotic resistance profile of five *S. aureus* isolates (Nugroho *et al*., 2016)

Antibiotics	*S. aureus*				
	ATCC 25923	8212	1656	1787	4734
Chloramphenicol	S	S	S	S	**R**
Gentamicin	S	S	**R**	S	S
Erythromycin	S	S	**R**	S	S
Ciprofloxacin	S	S	**R**	**R**	S
Tetracycline	S	S	**R**	**R**	S
Benzyl penicillin	S	S	**R**	**R**	S
Oxacillin	S	S	**R**	S	S
Levofloxacin	S	S	**R**	S	S
Moxifloxacin	S	S	**R**	S	S
Clindamycin	S	S	**R**	S	S
Dalfopristin	S	S	S	S	S
Linezolid	S	S	S	S	S
Vancomycin	S	S	S	S	S
Tigecycline	S	S	S	S	S
Nitrofurantoin	S	S	S	S	S
Rifampicin	S	S	S	S	S
Trimethoprim sulfamethoxazole	S	S	S	S	S

S = sensitive, R = resistant

The resistance patterns observed in some strains are primarily attributable to the mecA-encoded penicillin-binding protein 2a (PBP2a), which lowers β-lactam affinity and allows peptidoglycan cross-linking to continue at inhibitory drug levels. Additional mechanisms frequently co-occur, including β-lactamase production (blaZ), biofilm formation, and O-acetyltransferase A (OatA)-mediated peptidoglycan O-acetylation, which together diminish effective antibiotic activity (Sanchez *et al*., 2017). These combined mechanisms preserve cell-wall synthesis and reduce the effective antibiotic concentration at target sites, aligning with clinical observations that under high selection pressure and broadened resistance spectra, treatment success declines (Habboush & Guzman, 2023; Liu *et al*., 2024; Sanchez *et al*., 2017; Sari *et al*., 2024).

The inter-isolate variation observed in Table 1 supports the need for ongoing local susceptibility testing before selecting empirical regimens. The regional context, in line with local patterns, indicates a trend of increasing resistance and clinical burden, so the residual susceptibility of certain agents provides an opportunity for non-antibiotic use and combination strategies to become more rational. A direct implication of this pattern is the need to explore bacteriophages as a precision therapeutic candidate that operates outside conventional drug targets and has the potential to suppress MDR isolates (Liu *et al*., 2024; Murray *et al*., 2022; World Health Organization, 2022).

Phage Specificity Test Against *S. aureus*

Table 2 shows the host range of three phage isolates (FSb, FSs, FSk) on fourteen test bacterial strains. Of the fourteen *S. aureus* strains tested, the three phages lysed only four (ATCC 25923, 1758, 4713, 8212) and showed no activity on isolate 1656 or on non-target bacteria such as *S. epidermidis* and *E. coli*, confirming receptor specificity (Górski *et al*., 2018; Yehl *et al*., 2019). This pattern reinforces the phages' characteristic specificity toward distinct surface receptors among strains.

Host range specificity is an interaction between phage tail proteins and bacterial cell wall receptors. Structural changes in receptors in certain isolates can hinder adsorption, preventing successful phage infection in those strains. The failure to lyse strain 1656, despite it being the same species, supports the hypothesis of variation in surface receptors or peptidoglycan structure that affects phage adsorption and

endolysin access (Bernard *et al*., 2011; Sanchez *et al*., 2017). This characteristic is advantageous for precision therapy because it minimizes disruption of the microbiota, but it requires mapping of target receptors and phage–isolate compatibility testing before application (Abedon *et al*., 2021; Brives & Pourraz, 2020; Liu *et al*., 2024).

Table 2. Host range of phages FSb, FSs and FSk (Nugroho, 2017)

Bacterial strain	Phage		
	FSb	FSs	Fsk
S. aureus ATCC 25923	+	+	+
S. aureus 1758	+	+	+
S. aureus 4713	+	+	+
S. aureus 8212	+	+	+
S. aureus 1656	-	-	-
S. epidermidis	-	-	-
S. hominis	-	-	-
S. mutans	-	-	-
Bacillus	-	-	-
Escherichia coli	-	-	-
Klebsiella pneumoniae	-	-	-
Pseudomonas aeruginosa	-	-	-
Salmonella	-	-	-

The limitation of host range can be overcome by formulating cocktails that combine multiple phages with different target receptors, or through genetic engineering of phage tail fiber proteins to expand the host spectrum. This approach has been shown to increase coverage and reduce the likelihood of resistance emerging against a single phage. Clinically, this implies the need to design phage combinations based on the molecular characteristics of local isolates, as well as *in vitro* evaluations that simulate clinical conditions (Brives & Pourraz, 2020; Liu *et al*., 2024; Mitsunaka *et al*., 2022).

In vitro Lytic Activity of Bacteriophages

Figure 1 shows the dynamics of the decline in *S. aureus* CFU/mL after treatment with phages FSb, FSs, and FSk using the total plate count (TPC) method over eight hours. Phage FSs produced the steepest decline within the first four hours and maintained it through the eighth hour. FSb and FSk displayed intermediate activity with a more gradual slope of the curve.

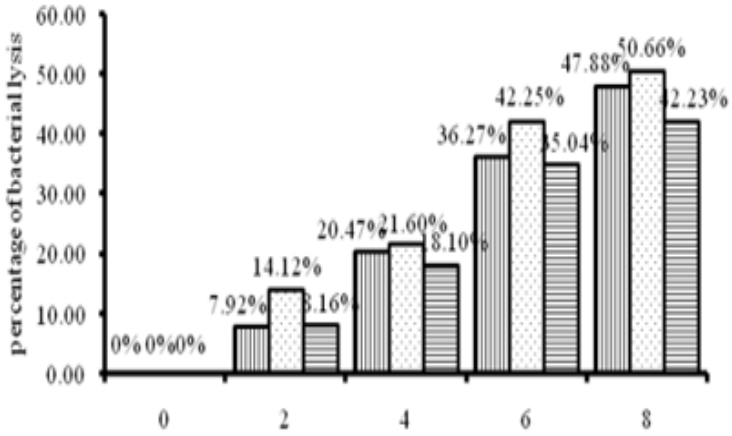

Figure 1. Presentation of the lysis process of *S. aureus* by phages FSb, FSs, and FSk (Nugroho, 2017)

The rapid lysis kinetics observed with FSs indicate efficient adsorption, a short latent period, and effective endolysin/CHAP activity against S. aureus peptidoglycan. Holin encoded

by the phage genome accumulates in the cytoplasmic membrane, creating large pores and allowing endolysin to reach the peptidoglycan to trigger lysis. This combination of factors accelerates the lytic cycle and hastens the decline of the bacterial population in the early phase (Abdelrahman et al., 2021; Brüser & Mehner-Breitfeld, 2022; Young, 2002).

Although the in vitro model shows strong bactericidal potential, it does not represent biological barriers such as biofilms, tissues, and host immune responses. Therefore, this data needs to be followed by Ex Vivo/in vivo tests to ensure clinical translation, including evaluation of repeated dosing regimens and phage stability on wound surfaces. The therapeutic implication is an emphasis on designing protocols that consider the dynamics of the target environment (Duarte et al., 2021; Habboush & Guzman, 2023; Liu et al., 2024).

Bacteriophage Activity Against S. aureus Biofilm

Figure 2 shows the variability of biofilm biomass responses among twenty clinical S. aureus strains, all of which formed biofilms within 24 hours. The two phages used produced opposite outcomes. Phage vB_SauP-436A reduced biofilm biomass in four strains, whereas vB_SauM-515A1 increased biofilm biomass in five strains despite being effective against planktonic cells. This finding indicates that the success of phage therapy on biofilms does not always align with its effectiveness on free cells (Liu et al., 2024).

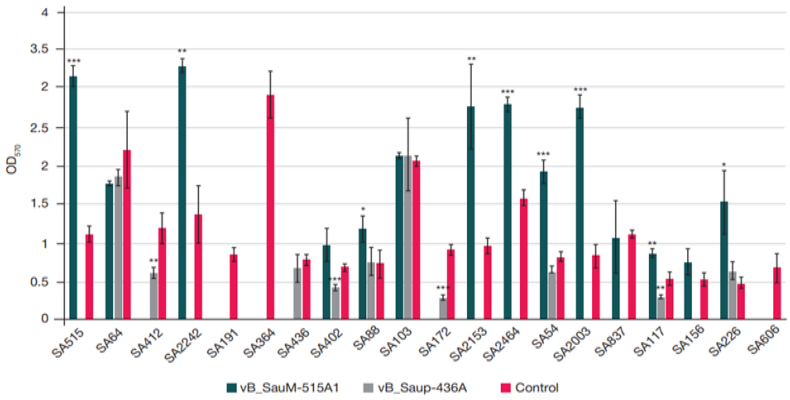

Figure 2. The ability of each bacterial strain to produce biofilm within 24 hours (Abdraimova *et al*., 2024)

Differences in phage responses are likely determined by the compatibility of lytic enzyme domains with biofilm matrix components (e.g., PNAG) and the ability of the phages to penetrate mature biofilms. In some conditions, phage exposure can trigger a bacterial stress response that increases matrix production, leading to greater biofilm biomass. This fact underscores the need to select phages that have been specifically tested against the target biofilm, not just against planktonic cells (Abdraimova et al., 2024; Duarte et al., 2021; Oliva et al., 2021).

Strategies to enhance effectiveness can include combining phages with matrix-degrading enzymes or using cocktails that target multiple biofilm components at once. This approach has the potential to reduce recurrence and improve eradication in chronic infections dominated by biofilms. The clinical implication is a call for preclinical testing that evaluates biofilm-specific outcomes before proceeding to clinical trials (Anyaegbunam et al., 2022; Duarte et al., 2021; Liu et al., 2024).

Ex Vivo Evaluation on Porcine Burn Wound and Human Skin Models

In porcine and human skin models, phages ISP and RPCSa2 quickly suppressed MRSA. Figure 3 shows that a single phage dose (up to 10^8 PFU/mL) significantly reduced the MRSA burden within the first two to four hours. Figure 4 illustrates that repeated administration every two to four hours maintained a more stable suppression of bacteria up to 24 hours, especially on human skin. Figure 5 demonstrates a prophylactic effect, where applying phages one hour prior to inoculation significantly prevented colonization, nearly reaching the detection limit

under optimal conditions. The effect on biofilm structure is crucial to determine how far phages can penetrate and destroy biofilms formed by multidrug-resistant *Staphylococcus aureus*. One relevant study by (Abdraimova *et al*., 2024) evaluated the effectiveness of two lytic phages against the biofilms of twenty clinical *S. aureus* strains, including MRSA and MDR. The first method, carried out by treating with a single phage (Figure 3). The second method, involved repeated phage administration at 2–4-hour intervals (Figure 4). The third method, assessed prophylactic application, with phages applied 1 h prior to inoculation (Figure 5).

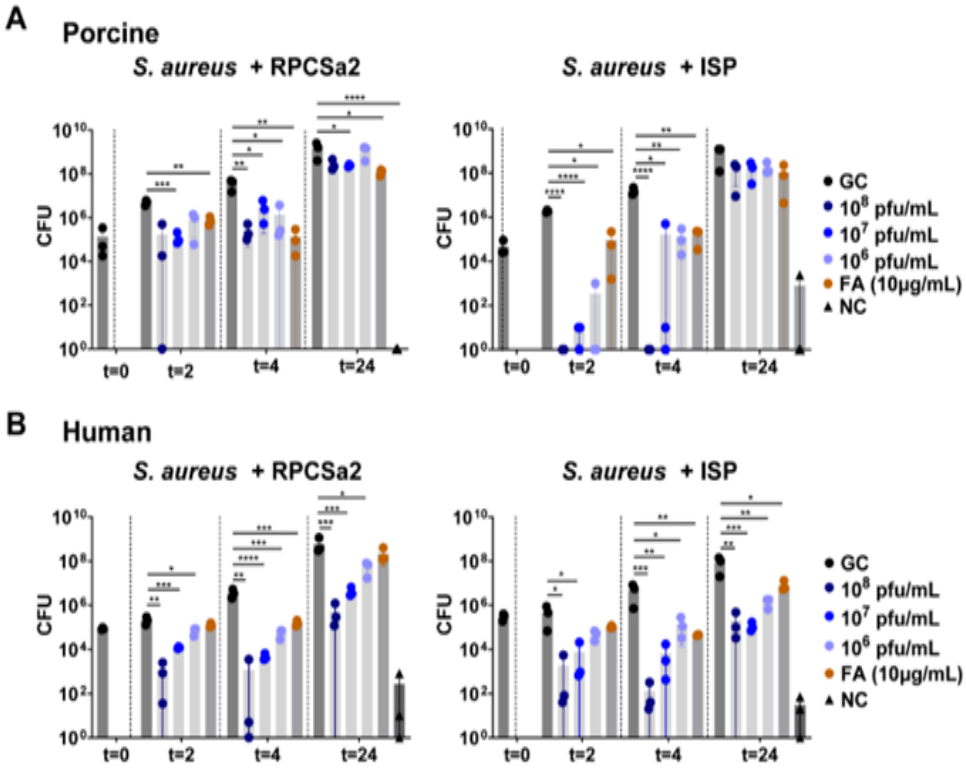

Figure 3. Bacterial growth after single dose (Molendijk *et al*., 2024)

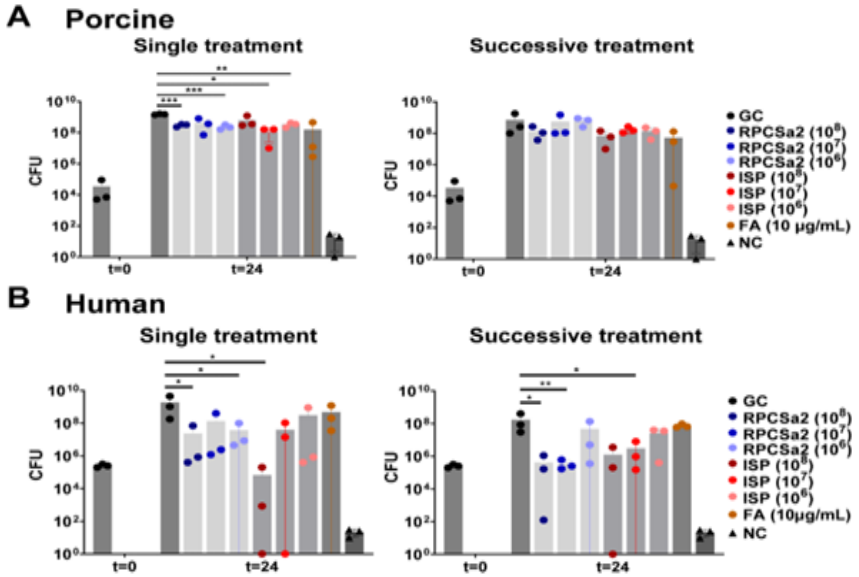

Figure 4. Bacterial growth after single and repeated doses (Molendijk *et al*., 2024)

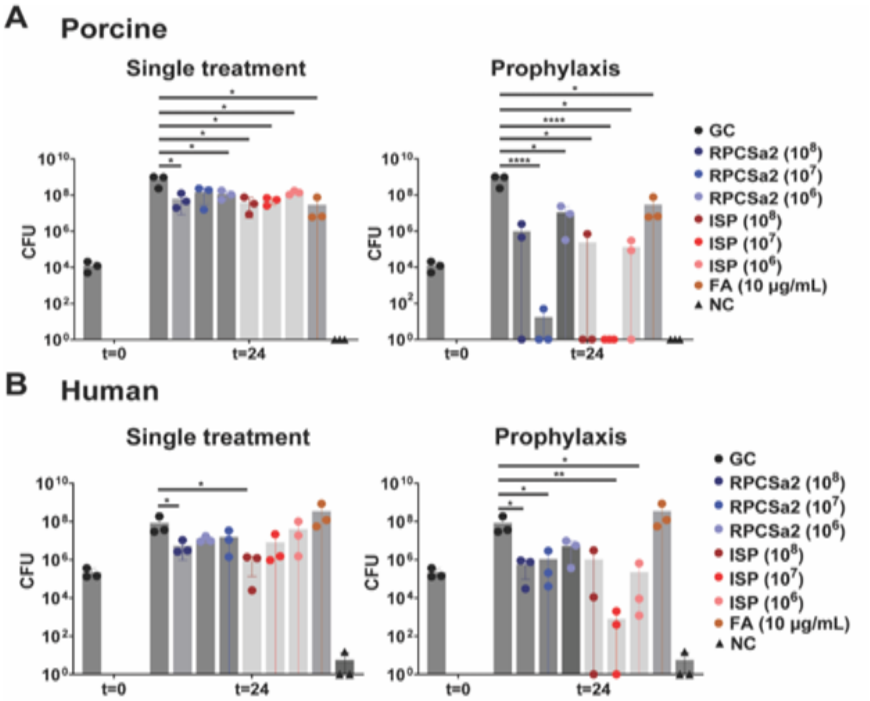

Figure 5. Bacterial growth after single dose and under prophylactic phage treatment (Molendijk *et al*. 2024)

The dose-response pattern and the benefit of repeated regimens confirm that phage density on the wound surface is a primary determinant of therapeutic success. High doses accelerate initial contact and increase the probability of first-cycle lysis, whereas repeated administration compensates for titer declines due to diffusion, local degradation, or tissue absorption. These data align with phage kinetics theory and provide a practical basis for establishing dosing intervals in topical applications (Brives & Pourraz, 2020; Liu et al., 2024; Molendijk et al., 2024).

The success of prophylaxis opens opportunities for using phages in high-risk scenarios such as extensive burn wounds, surgical procedures, or intensive care settings with heavy MRSA colonization. However, clinical trials remain necessary to evaluate safety, local immunogenicity, and interoperability with wound dressings or topical antibiotics. The clinical implication underscores integrating phage therapy into evidence-based wound care protocols (Brives & Pourraz, 2020; Liu et al., 2024; Molendijk et al., 2024).

Future Directions

The latest approaches in utilizing bacteriophages through synthetic engineering have become an important strategy to overcome the limitations of natural phages, especially in infections by resistant Staphylococcus aureus. A bacteriophage engineering approach based on genetic synthesis without isolating an intact phage has established a new foundation in the development of therapies against resistant bacterial infections (Ando et al., 2015). (Ando, 2020) In subsequent developments, the Synthetic Engineering Platform 2.0 was designed to assemble phage genomes from synthetic DNA fragments and activate them into functional phages through a cell-free rebooting system (Ando, 2022).

This technology enables various genetic modifications such as expanding host range through tail fiber gene mutagenesis, removing toxic genes, and integrating biological containment systems that prevent phages from spreading beyond the target system, without reducing their effectiveness in killing bacteria (Mitsunaka et al., 2022). This innovation accelerates the design process of therapeutic phages and enhances molecular control over phage composition, making it a rational and adaptive solution to confront resistant pathogens like MRSA and strains expressing O-acetyltransferase A (OatA) (Shimamori et al.,

2021).

Conclusion

Bacteriophages offer a promising therapeutic alternative against resistant Staphylococcus aureus, especially MRSA, through specific lytic activity mediated by endolysin and holin genes. However, phage effectiveness is influenced by several molecular and structural resistance factors, such as the presence of the PBP2a protein encoded by the mecA gene, peptidoglycan modifications by the OatA enzyme, and complex biofilm formation. In vitro findings show that phages successfully reduce S. aureus populations, whereas Ex Vivo tests on burned skin confirm that phages whether in single, repeated, or prophylactic applications are significantly able to suppress MRSA colonization more effectively than topical antibiotics. Interestingly, the phage response to biofilm is strain- and phage-specific: phage vB_SauM-515A1 increased biofilm biomass in some strains, whereas vB_SauP-436A was able to significantly reduce it, indicating that a phage's activity against biofilm cannot be predicted solely from its lytic ability against planktonic cells. Therefore, the future development of therapeutic phages must consider phage interactions with biofilms and modified cell wall structures, as well as utilize synthetic engineering technology to expand host range and enhance therapeutic precision. Such approaches are expected to effectively and sustainably address the challenges of multidrug-resistant bacterial infection therapy.

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