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Review Article **Pharmacy**

Therapeutic Microbes Against Drug-Resistant Pathogens: A Comprehensive Narrative Review

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Abstract

Antimicrobial resistance (AMR) poses an immense worldwide health threat, predicted to result in as many as 10 million mortalities by 2050. With the stagnation of antibiotic discovery as well as the rapid growth of multidrug-resistant pathogens, novel therapeutic strategies are urgently required. Microbes engineered or naturally therapeutic—offer innovative approaches for targeted pathogen elimination. These include bacteriophage therapy, engineered probiotics, synthetic biology-based organisms, and microbial consortia. This review synthesizes recent advances, evaluates their clinical potential, and highlights the limitations, regulatory obstacles, and future potential for these novel therapies. Collectively, microbial-based interventions represent a promising, yet underutilized, frontier within the fight over AMR.

Keywords: Antimicrobial resistance; engineered microbes; bacteriophage therapy; synthetic biology; probiotics; microbiome therapeutics.

INTRODUCTION

Antimicrobial resistance (AMR) is considered among the most critical challenges to worldwide wellness, security of food, and prosperity. The World Health Organization (WHO) predicts that by 2050, deaths due to AMR may surpass those from cancer, reaching up to 10 million per year (Pal *et al.*, 2020). The reduction in the identification of novel antibiotics, coupled with the rapid rise of multidrug-resistant (MDR) bacteria, underscores the urgent need for innovative treatment approaches (Yang & Chen, 2021).

Microbes themselves offer a promising alternative strategy for combating resistant pathogens. This concept is rooted in the ecological principle of microbial competition. Harnessing beneficial or engineered microbes to directly target harmful bacteria is gaining increasing attention. Therapeutic approaches include bacteriophage therapy, engineered probiotics, microbial consortia, and synthetic biology-derived microbes designed to detect and kill pathogens (Cui *et al.*, 2024; Kakkar 2024; Qin & Li, 2022).

Despite promising preliminary results, current research is fragmented. There has not yet been a comprehensive review focusing on engineered or therapeutic microbes specifically designed to eliminate drug-resistant bacteria in human hosts. This article addresses this gap by providing a detailed review of the available literature, assessing therapeutic potential, limitations, and future research directions.

METHODS

This review followed a systematic search of literature utilizing PubMed, Scopus, Embase, and Web of Science. Keywords included “engineered bacteria,” “synthetic biology,” “bacteriophage therapy,” “therapeutic probiotics,” and “antimicrobial resistance.” Inclusion criteria were human and translational studies published between 2015 and 2025. Exclusion criteria were animal-only studies and purely computational models. Articles were screened for relevance and quality before inclusion.

- **Bacteriophage Treatment**

Bacteriophages are germs that exclusively target microorganisms. Their therapeutic use dates back to the early 20th century, with renewed interest in recent decades as MDR pathogens emerged (Hatfull, 2022; Kim *et al.*, 2025). Recent clinical applications include treatment of Pseudomonas aeruginosa in cystic fibrosis, and Staphylococcus aureus bacteremia (Sawa *et al.*,

2024; Olawade *et al.*, 2024). Limitations include narrow host range, regulatory barriers, and potential immune responses.

- **Engineered Probiotics**

Engineered probiotics, including genetically modified Escherichia coli Nissle 1917 and Lactobacillus strains, were explored in living therapeutics. These microbes can be programmed to secrete antimicrobial peptides or modulate host immunity (Do *et al.*, 2024; Liu *et al.*, 2024; Mejia-Pitta *et al.*, 2021). Applications include prevention of Clostridioides difficile infection and suppression of gut MDR bacteria.

- **Synthetic Biology Approaches**

Synthetic biology allows the design of microbes equipped with genetic circuits to detect pathogens and respond with targeted killing mechanisms. Examples include CRISPR-Cas guided antimicrobials, kill-switch engineered microbes, and hybrid phage-bacteria systems (Qin & Li, 2022; Shim, 2023; Shim, 2025; Lobocka *et al.*, 2021). These approaches promise high specificity but require careful safety controls.

- **Microbial Consortia and Microbiome Transplantation**

Microbial consortia, or combinations of beneficial strains, offer synergistic effects in pathogen suppression. Fecal microbiota transplantation (FMT) is a successful clinical application for recurrent Clostridioides difficile infection (Vindigni & Surawicz, 2017; Flores-Treviño *et al.*, 2025). However, risks include transfer of undesired resistance genes and variability in donor material.

- **Conceptual Figure**

This diagram illustrates how bacteriophages, engineered probiotics, synthetic microbes, and microbial consortia contribute to the elimination of resistant pathogens and restoration of microbiome balance.

Table -1: Summary of Key Studies

Author (Year)	Microbe Type	Target Pathogen	Main Findings
Dedrick *et al.*, (2019)	Engineered Bacteriophages	Mycobacterium abscessus	Successful compassionate use case; bacteriophage therapy led to clinical improvement.
Do *et al.*, (2024)	Engineered Probiotics	Enteric pathogens	Synthetic probiotic overcame pathogen defenses and enhanced gut colonization resistance.
Sawa *et al.*, (2024)	Phage- based immunotherapy	Acute viral infections	Evaluation in the clinical phage therapy cases showing safety and potential efficacy.
Mimee *et al.*, (2016)	Synthetic Microbes	Various MDR bacteria	Synthetic biology approaches proposed for precision microbiome therapeutics.
Cui *et al.*, (2024)	Phage Therapy	Pseudomonas, Staphylococcus	Comprehensive review supporting potential clinical applications of phage therapy.

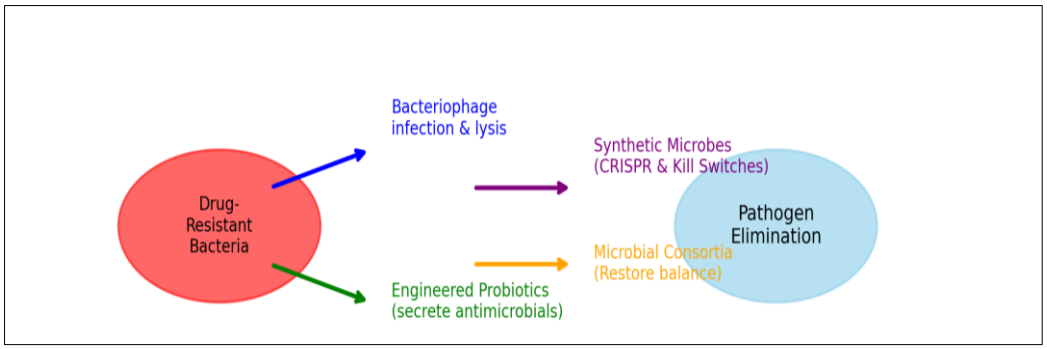

Figure 1: Mechanisms of therapeutic microbes against drug-resistant bacteria

- **Summary of Key Studies**

Table 1 shows the summary of existing studies.

DISCUSSION

Microbial therapies represent an innovative paradigm shift in the fight against AMR. Current evidence suggests promising efficacy across different modalities, particularly bacteriophage therapy and engineered probiotics. However, large-scale randomized controlled trials are scarce. Challenges include regulatory approval, biosafety concerns, scalability, and public acceptance.

Future research should prioritize developing standardized protocols, integrating synthetic biology for precision targeting, and conducting head-to-head trials with conventional antibiotics. The combination of microbial therapies with antibiotics may also provide synergistic effects and delay resistance development. Ethical considerations also require attention, including biosafety concerns, horizontal gene transfer risks, and

the potential ecological impact of releasing engineered microbes. Furthermore, compassionate use cases in cystic fibrosis and Mycobacterium abscessus demonstrate both the promise and limitations of microbial therapeutics. Global health policy should prioritize funding frameworks, regulatory pathways, and international collaborations to ensure safe development and deployment of these therapies.

CONCLUSION

Therapeutic microbes provide a compelling alternative to traditional antibiotics in addressing the AMR crisis. This review highlights their potential applications, current limitations, and future opportunities. While early evidence is encouraging, rigorous clinical trials and regulatory frameworks are essential before widespread implementation. In addition, policymakers and healthcare systems must develop clear regulatory pathways, invest in translational research, and support large-scale clinical trials to accelerate clinical adoption.

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