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Resistance redefined: Exploring symbiotic networks in microbial survival

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The emergence of antimicrobial resistance poses a profound global health challenge that extends beyond classical models of mutation and antibiotic selection. In this context, the Resistance Symbiosis Hypothesis is proposed to suggest that bacteria enhance their resistance capabilities through symbiotic relationships with other microorganisms, including fungi and viruses. This perspective introduces a broader ecological framework for understanding antimicrobial resistance, emphasizing cooperation and interdependence within microbial communities rather than isolated bacterial adaptation.

Symbiotic interactions among microorganisms are well documented across biological systems. Bacterial endosymbionts in insects provide essential nutrients and metabolic support, demonstrating how close microbial partnerships can enhance host survival[1]. Similarly, bacteria and fungi frequently coexist within biofilms, forming structured and resilient communities that promote persistence under environmental stress[2]. Within this hypothesis, bacteriophages play a central role by facilitating horizontal gene transfer through transduction, enabling the dissemination of antibiotic resistance genes across bacterial species and accelerating adaptation in hostile environments[3].

Bacteriophages are uniquely suited to act as vectors for resistance due to their ability to infect multiple bacterial hosts and integrate into bacterial genomes as prophages. This integration not only introduces new genetic material but may also enhance bacterial fitness under selective pressures such as antibiotic exposure. Phage-mediated gene exchange may therefore represent a dynamic and efficient mechanism through which resistance traits are stabilized and amplified within microbial populations.

Beyond gene transfer alone, resistance symbiosis may involve complex inter-microbial signaling networks. Bacteria and phages may utilize quorum sensing molecules or other chemical signals to coordinate resistance responses at the community level, optimizing gene exchange and resource allocation during antimicrobial stress. Fungi may further contribute by acting as structural scaffolds within biofilms, facilitating closer physical proximity between bacteria and phages, or serving as reservoirs for resistance determinants, thereby forming a functional fungal–bacterial–phage triad that enhances collective survival.

Metabolic interdependencies within these symbiotic consortia may also indirectly promote resistance. Microbial partners can share metabolic pathways or produce protective metabolites that degrade antibiotics or create localized protective niches. In addition to genetic mechanisms, such relationships may influence non-genetic resistance strategies, including phenotypic plasticity, biofilm-associated tolerance, and stress-induced adaptive states that allow bacteria to survive antimicrobial exposure without permanent genetic change.

Phage-induced stress responses represent another potential layer of resistance regulation. Phage infection may trigger bacterial stress pathways that upregulate resistance-associated genes, while extracellular vesicles produced by bacteria or fungi could serve as vehicles for transferring resistance genes or signaling molecules across species boundaries[4]. These vesicles may function as mobile resistance units, further reinforcing interspecies cooperation within microbial ecosystems.

Testable predictions derived from the Resistance Symbiosis Hypothesis include: (i) disruption of fungal or phage partners within polymicrobial communities will significantly reduce bacterial resistance levels; (ii) experimental inhibition of inter-microbial signaling pathways will attenuate horizontal transfer of resistance genes; and (iii) removal of key metabolic partners will increase

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bacterial susceptibility to conventional antibiotics *in vitro* and *in vivo*.

Understanding resistance as an emergent property of microbial symbiosis opens new avenues for therapeutic intervention. Targeting both bacterial pathogens and their symbiotic partners, including phages and fungi, may provide dual-action or multi-target strategies to disrupt resistance networks. Strategies could include modifying phage therapy to interfere with symbiotic interactions[5], and exploiting fungal–bacterial dependencies within biofilms could sensitize microbial communities to existing antimicrobials[6].

Counterpoints to this hypothesis include the argument that classical mutation-selection dynamics alone may sufficiently explain many resistance patterns, and that not all microbial communities display stable or cooperative symbioses. Additionally, horizontal gene transfer can occur independently of long-term symbiotic relationships, suggesting that symbiosis may amplify but not exclusively drive resistance evolution. Ultimately, the Resistance Symbiosis Hypothesis offers a conceptual framework for rethinking antimicrobial resistance as a community-driven phenomenon, encouraging the development of innovative, ecology-informed strategies to address this escalating global crisis.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Al-Khikani FHO conceptualized and developed the study design, reviewed the literatures, took part in proposal development, led the data collection and data entry, and took part in data analysis and interpretation, manuscript writing and review. Ayit AS also conceptualized and developed the study design, participated in data analysis and interpretation, engaged in proposal development, and contributed to manuscript preparation and review. All authors have read and approved the final version of the manuscript.

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Erratum:Health and environmental impacts of Gaza conflict (2023–2024): A review

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The authors would like to correct an error in the Abstract of the original article. The original sentence reads: "The conflict claimed over 36 000 Palestinian lives, with women and children making up 70% of the casualties, and resulted in more than 80 000 injuries". The sentence should have read: " The conflict claimed over 40 000 Palestinian lives, with women and children making up 70% of the casualties, and resulted in more than 90 000 injuries". The error does not affect the conclusion of the study. The authors apologize for the error and the inconvenience it might have caused to readers.