

Antibiotic adjuvants: A promising approach to overcome antibiotic resistance



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Abstract

The problem of antibiotic resistance is on the rise, with multidrug-resistant strains emerging even to the last resort antibiotics. In such a scenario, it is prudent to delve into the varying mechanisms of resistance to existing antibiotics and target them to improve antibiotic efficacy. Non-antibiotic compounds called antibiotic adjuvants which target bacterial resistance can be used in combination with obsolete drugs for an improved therapeutic regime. The field of “antibiotic adjuvants” has gained significant traction in recent years where mechanisms other than β -lactamase inhibition have been explored. The major focus of this review is how to target these resistance mechanisms by the use of antibiotic adjuvants. Different types of direct acting and indirect resistance breakers are discussed including enzyme inhibitors, efflux pump inhibitors, inhibitors of teichoic acid synthesis, and other cellular processes. Antibiotic–adjuvant combinatorial therapy indeed has immense potential to be used as an upcoming orthogonal strategy to conventional antibiotic discovery.

1. Introduction

Microbial infections are one of the most serious risks to public health globally, putting significant cost strain on global healthcare. Antimicrobial resistance (AMR) contributed to the current issue (1). According to a recent analysis, Antimicrobial resistance (AMR) kills roughly 0.7 million people per year, which is anticipated to rise to 10 million by 2050 (2). This would impose a significant burden on global spending on healthcare. Even after launching the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015, lower respiratory tract infections and diarrheal diseases were among the top ten worldwide causes of mortality in 2019, accounting for 4 million fatalities (3).

Rather than investing in random semi-synthetic adaptations of existing medications, it is better to recycle the present antibiotic arsenal by targeting particular causes of resistance and conquering them. Physical compound combinations provide structural and mechanistic understanding that may be used to develop sensible semi-synthetic changes. As a result, antibiotic development would be more simplified. Aside from combinations of two active compounds, another interesting class of combinations is those composed of an antibiotic and a non-antibiotic molecule that only targets the mechanism of resistance to the said antibiotic, indirect resistance elements, or nonessential resistance pathways. This combination would eliminate the redundant usage of an antimicrobial by making it beneficial in the treatment of multidrug-resistant types of bacteria (4, 5).

Combinations of β -lactam/ β -lactamase inhibitors, for example, are clinically approved and

more are under clinical studies. Given the effectiveness of these combinations, it is worthwhile to investigate new mechanisms of resistance that may be addressed by similar compounds in order to restore the efficacy of existing antibiotics. These substances are known as "antibiotic adjuvants" because they have little or no antibiotic action (6).

2. Antibiotic adjuvants

Antibiotic adjuvants are compounds that enhance the action of current antibiotics by reducing or directly inhibiting resistance mechanisms. The concept of antibiotic adjuvants stems from clinically effective combinations of two or more antibiotics. These have been empirically employed to produce synergy, broaden the range of activity, and overcome resistance. In contrast to traditional antibiotic combinations, antibiotic adjuvants have no or little antibacterial action on their own. Antibiotic adjuvants can be roughly characterized as direct, indirect, or host-modulating resistance breakers based on their target profile. To potentiate antibiotics, antibiotic adjuvants target many active and passive resistance mechanisms in bacteria. All these different types of resistance breakers are discussed in the subsequent sections (6).

2.1 Direct resistance breakers

These are Class I adjuvants that function with antibiotics on resistance-causing bacterial targets. These adjuvants directly suppress antibiotic resistance mechanisms such as inhibiting enzymes, efflux pumps, or new targets that compensate for the original targets. The only clinically approved adjuvants in use now are β -lactamase inhibitors, which inactivate β -lactamases (7).

2.2 Indirect resistance breakers

Antibiotic resistance in bacteria can be caused by an inherent genetic connection, physiological variables, or the presence of generic treatment evasion mechanisms. These comprise a variety of interdependent aspects that are critical for bacterial resistance components. These characteristics, in addition to the actual aspects of resistance, can be possible targets for creating adjuvants. Through this technique, antibiotic action can be resurrected by discovering non-evident synergy in the enormous nonessential gene space. Membrane-targeting chemicals are another type of adjuvant that can have many effects such as inhibiting efflux machinery and permeabilizing the bacterial membrane for antibiotic penetration (7, 8).

2.3 Adjuvants targeting host processes

The potency of antibiotics within infected organisms can be improved by using a number of host defence mechanisms. Antibiotics, for example, have been demonstrated to function well together and can even boost antibiotic activity in difficult-to-treat biofilms. These peptides have a wide variety of strengths in terms of potent antibacterial activity or Class Ib adjuvant capabilities, as well as Class II adjuvant properties. These immunomodulatory peptides influence the host immune system in a number of ways, including lowering inflammation to prevent an infection from eliciting an overly aggressive immunological response that leads to sepsis and stimulating host-cell-based antimicrobial actions such as enhanced phagocytosis (9).

3. Future perspective

In order to combat complex types of infection, such as bacterial biofilms, metabolically

suppressed bacterial subpopulations like stationary phases or persister bacteria, and intracellular infections, antibiotic-adjuvant combinations need also be researched. This would make it possible to use it in actual therapeutic settings. This would additionally require for a detailed examination of the precise mechanism underlying such combination activity and the impact adjuvants have on the pathogenicity and quorum sensing of bacteria. Additional effects such as immunomodulation, induction/inhibition of autophagy, quorum sensing and pathogenicity, influence on intracellular pathogens, etc. would be an interesting area to investigate, especially for tiny molecule membrane targeting adjuvants and other indirect resistance breakers. Further research and development in this field could lead to the development of novel and effective treatments for infectious diseases, benefiting patients in the future.

4. Conclusions

Recent study has shown that adjuvant treatment can be used to combat multiple mechanisms of antibiotic resistance in bacteria. Direct resistance breakers, indirect resistance breakers, and host-modulating agents are among them. Direct resistance breakers, particularly β -lactamase inhibitors, have been the most effective class of adjuvants to date, with several being authorized for clinical use. Concurrently, continued attempts to fill gaps in approved adjuvants are generating results, with new candidates appearing in clinical trials.

References

1. McCloskey B, Dar O, Zumla A, Heymann DL. Emerging infectious diseases and pandemic potential: status quo and reducing risk of global spread. *The Lancet infectious diseases*. 2014;14(10):1001-10.
2. Top Ten causes of death. 2020. <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (accessed July 26, 2023).
3. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022. 2022. <https://www.who.int/publications/i/item/9789240062702> (accessed July 26, 2023).
4. Tyers M, Wright GD. Drug combinations: a strategy to extend the life of antibiotics in the 21st century. *Nature Reviews Microbiology*. 2019;17(3):141-55.
5. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nature reviews microbiology*. 2015;13(1):42-51.
6. Wright GD. Antibiotic adjuvants: rescuing antibiotics from resistance. *Trends in microbiology*. 2016;24(11):862-71.
7. Ashwath P, Sannejal AD. The Action of Efflux Pump Genes in Conferring Drug Resistance to Klebsiella Species and Their Inhibition. *Journal of Health and Allied Sciences NU*. 2021;12(01):24-31.
8. Ahmad A, Hussain S, Mehmood R, Rana A, Mustafa G. Antibiotic Resistance Breakers and Nano-Antibiotics in Mediating Antimicrobial Resistance [Internet]. *Antibiotic Resistance - New Insights [Working Title]*. IntechOpen; 2023. Available from: <http://dx.doi.org/10.5772/intechopen.111761>
9. Dhanda G, Acharya Y, Haldar J. Antibiotic Adjuvants: A Versatile Approach to Combat Antibiotic Resistance. *ACS omega*. 2023;8(12):10757-83.