

Advanced and innovative therapeutic strategies for unveiling the battle of antibiotic resistance



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1. Introduction to Antibiotic Resistance

1.1 A Brief History

Antibiotics (AB), the term coined in the year 1941 has come a long way as an effective pharmacological agent in the history of integrative medicine. Antibiotic resistance is quite common which was observed for *S.aureus* within 5 years after introduction of first antibiotic i.e., penicillin in 1943. The truth is, the usage of AB has eventually resulted in resistance over time and are now rendered obsolete. Bacterial infection is tied to a large part of morbidity and mortality rates in medical practice and antibiotics have proved to be a boon resolving this problem. However, antibiotic resistance (ABR) has now become a massive issue with social, economic and health repercussions (1). Figure 1 depicts the mechanisms exploited by bacteria in order to tackle the action of antibiotic agents. The statistic claims that by 2050 the AMR population could reach over 10 million people thus exceedingly around 8.2 million lives which is currently accounted to cancer (2,3). This newsletter focuses on the therapeutic approaches and extensive attempts that are made to overcome for antibiotic resistance. Figure 2 depicts the underutilised tools such antibodies, stem cells, vaccines, immunomodulators and nanomedicines against antibiotic resistant.

2. Therapeutic approaches for combating antibiotic resistance

2.1 Development of new Antibiotics (Abs) with multi-effective and multidrug targets:

The ABR studies have shown that resistance to antibiotics that only target one protein emerges too quickly, shifting the concern towards development of antibiotics having multiple targets to act upon the drug candidates. The pharmacology of the drug generally speaks of its ability to interact with the multiple targets giving rise to two main categories, classified as multi effective and multi-functional. When a drug is associated with a single target but is an integral part of other process that depends on its inhibition, it is said to be multi effective. Whereas multifunctional agents have an extra antibacterial action in addition to their antibiotic target (4-6). Table 1 gives an overview of the antibiotics with their targets.

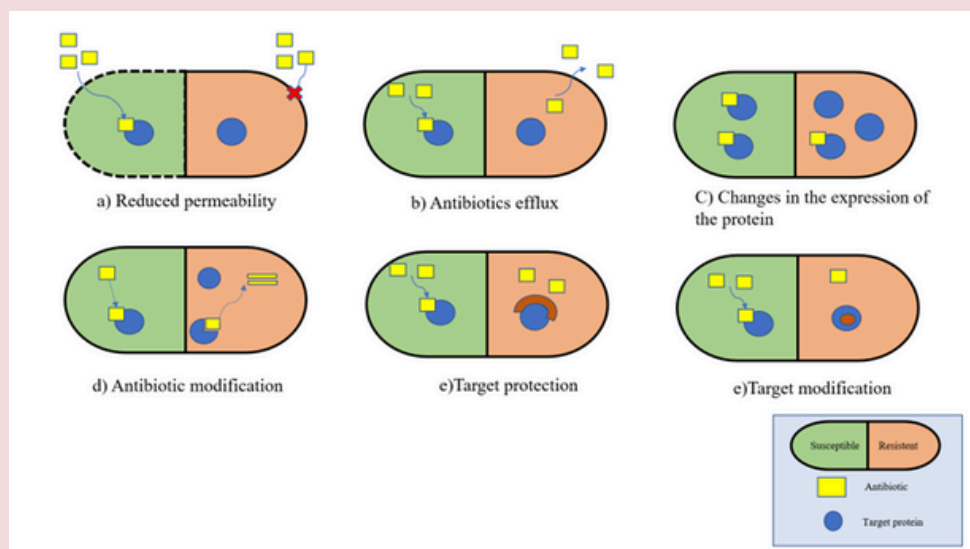


Figure 1: A graphical illustration of the mechanism of Antibiotic Resistance

2.2 Exploring nanomedicine as a therapeutic approach against AMB

Nanomedicine display characteristics feature of enhanced physicochemical property, prolongation of action and increased stability (14). For instance, liposomes were explored for its activity against intracellular strains where anti tubercular drugs were loaded within liposomes with tiny fabrications of ribonucleic acid. This system showed controlled release of drug with maximum concentration at the targeted site (15). Different liposomal types such as conventional liposomes, Fusogenic liposomes and surface modified liposomes (16-19). The most sophisticated variety of nanostructured lipid carriers are made of unstructured matrix with a blend of liquid oil matrix that reduces the rate of drug escape (20). Various lipids such as glyceryl monostearate, stearic acid, glyceryl behenate, tripalmitin are explored as a remedy to dela with antibiotic resistance (21-23). Nanosystems have notably prevented the promotion of resistance from bacteria by improving the therapeutic activity. Certain strategies that entail drug breakdown by lactamase, efflux pumps or thickening of bacterial cell walls involving nanosystems are explored widely as a therapeutic approach (24).

2.3 Immunomodulators as an alternative therapeutic approach against antibiotic resistance pathogens

Immunomodulators such as Host defence peptides (HDPs) having a broad-spectrum antimicrobial activity have been suitably used nowadays as a potential therapeutic agent to treat antibiotic resistant diseases. HDPs are component of innate immune system that comprises of three main classes such as linear α helical assembly excluding the disulfide bonds such as cathelicidins, magainins and cecropins, disulphide bridge stabilized β sheet assembly containing defensins and lastly a peptide in loop form. A self-promoted uptake mechanism explained by the pore forming ability of HDPs in the biological membrane demonstrates the cytotoxic functional abilities of such HDPs while some protection to cytotoxicity of HDPs is generally offered by the anionic phospholipids present in the mammalian membranes (25, 26).

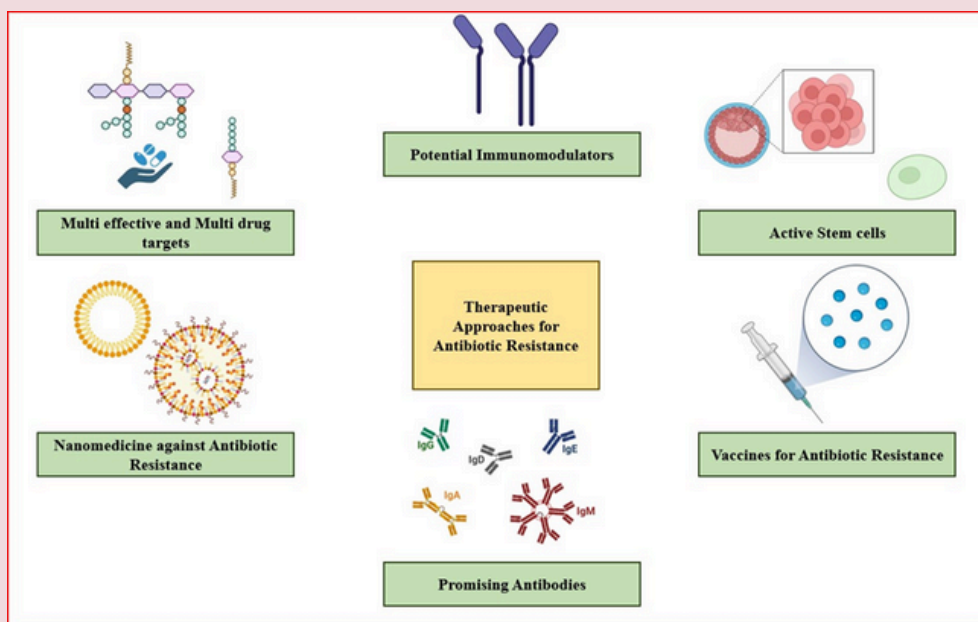


Figure 2. Therapeutic approaches as an alternative to tackle antibiotic resistance

Table 1. Summary of antibiotics with their mechanism of action to overcome ABR

S. No.	Antibiotic	Target	Mechanism of action	Ref
1.	Daptomycin	Phosphatidylglycerol, fluid lipid domains	Multi-effective- Inhibits the cell wall synthesis machinery by binding phosphatidylglycerol and then intruding into the fluid domains.	(7)
2.	Vancomycin	lipid II	Multi-effective Targets lipid II but also prevents formation of peptidoglycan and also prevents the creation of wall teichoic acid.	(8)
3.	Bacitracin	bactoprenol pyrophosphate	Multi-effective role ultimately results in inhibition of peptidoglycan and teichoic acid.	(9)
4.	Nitrofurantoin	cellular macromolecules	Multi-effective damages cellular macromolecules including DNA and membrane lipids	(10)
5.	Dapsone	dihydropteroate synthase	Multifunctional with anti-inflammatory and immunomodulatory activity	(11)
6.	Macrolides	50S rRNA	Depicts both anti-inflammatory and immunomodulatory multifunctional activity.	(12)
7.	Rifampicin	DNA-dependent RNA polymerase	anti-inflammatory and immunomodulatory	(13)

2.5 Stem cell in antibiotic resistance

Mesenchymal stem cells (MSCs) through production of antimicrobial factor appears to be a great non-antibiotic strategy for bacterial resistance. MSCs is proven to be immunomodulatory in nature and through this property it secretes immunomodulatory factors such as transforming growth factor- β , prostaglandin E2 and various antimicrobial peptides such as LL-37. Further it was seen and reported that antimicrobial peptide secreted by MSCs such as cathelicidin LL-37, hepcidin lipocalin etc indirectly led to inhibition of methicillin resistant S.aureus (30). Table 3 gives an overview of the mechanism of stem cell in antibiotic resistance.

2.6 Vaccines, particularly against antibiotic resistance bacteria (ARBs)

Prophylactic agents such as vaccines that have low probability of developing resistance and multitargeting ability proves to be the promising alternatives to the existing antibiotic treatment (33). Multiple immunogenic epitopes contained by vaccines as compared to a single targeting ability of antibiotics makes them superior in terms of developing resistance (34). The vaccine introduced against *S. pneumoniae*, and *Neisseria meningitidis* showed a complete elimination of antimicrobial resistance against these strains. Vaccines directly blocks the transmission of resistant strains of bacteria and decreases the usage of antibiotic and risk associated with acquiring and transmitting resistance (3, 35). Table 4 tabulates the advantages and disadvantages of various therapeutic approaches studied by the various scientists in combating the antibiotic resistance.

Table 3. Mechanism of stem cell in antibiotic resistance

Therapeutic approach	Mechanism	Target	Ref
Secretome from Mesenchymal stem cells (MSCs)	Inhibition of bacterial cell wall synthesis.	Antibiotic resistant Methicillin resistant <i>S.aureus</i> (MRSA)	(31, 32)
MSCs derived from human bone marrow and umbilical cord such as lipocal, hepcidin and LL-37	Act via a cationic antimicrobial peptide namely LL-37 expressed in the peroxidase-negative granules of neutrophils.	<i>E. coli</i> , <i>S. aureus</i> and <i>L. pneumoniae</i> and imipenem resistant <i>P. aeruginosa</i> in human infants	(31-33)

Table 4. Advantages and disadvantages of various therapeutic approaches in antibiotic resistance

Therapeutic approach	Advantage	Disadvantage	Ref
Host Defence peptides	Dual action: Direct killing of bacteria + Immunomodulatory action Multiple complementary actions responsible for minimal resistance	Prone to degradation by the protease enzyme due to presence of L-amino acids in their structure. Less bioavailability and faster elimination due to their small size. Systemic cytotoxicity towards host cells	(36)
Monoclonal antibodies	Attractive approach in immunocompromised or elderly population which do not response to vaccines Additive action shown by antibiotic and antibodies when co-administered simultaneously Specific and selectively target a pathogen by blocking the pathogen-host, protein-receptor interaction.	Recognizes a single target Large protein structure that limits the conformational binding of MAbs Expensive, less cost effective	(28)
Stem cells	Abundant in the human body and can be easily harvested	Risk of undesired immune responses, reaction at the administration site along with fear of disease transmission among the few	(32)
Vaccines	Highly specific Efficacious in immunocompromised patient through herd immunity High longevity as it has very less or no chance of developing resistance	Vaccine takes longer time i.e., few days or weeks to show its protective action compared to antibiotics Absence of animal models that are representative of human disease to test efficacy of vaccines.	(36, 37)

4. Conclusion

Antibiotic resistance is a complex issue posing significant threat to public health and has eventually resulted the easily treatable infections to a more complex and challenging stage. Therapeutic approaches overcoming antibiotic resistance emphasizes the importance of expanding the arsenal of treatment options for such infections along with rational prescription which is a recommended standard for thorough understanding of pharmacology and therapeutics. Exploring the multi-effective roles of antibiotics, nanosystem carriers entailing drug breakdown, immunomodulators expanding the horizon of antibiotic activity and synergistically acting monoclonal antibodies approaches in future will definitely be considered as a potent option to curtail the resistant factor. Thus, we conclude that, campaign with multidisciplinary strategy and constant oversighting of approaches for the therapeutic management of ABR is a possible remedy to battle antibiotic resistance. The clinical studies undergoing on these approaches will bring a new era in the treatment of resistant diseases.

Abbreviations

Antibiotic resistance (ABR)

Antibiotics (AB)

Host defence peptides (HDPs)

Monoclonal antibodies (MAbs)

Mesenchymal stem cells (MSCs)

Methicillin resistant S.aureus (MRSA)

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