

Approaches in the fight against Antibiotics resistance: Harnessing technology and biotechnology



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1. Introduction

Since their inception, antibiotics have been regarded as one of the most important discoveries of the twentieth century, and their widespread usage has transformed healthcare. Between 1950 and 1970, known as the "golden age" of antibacterial medication discovery, empirical screening of microbial natural product fermentation provided the majority of antibacterial classes currently utilized for infection treatment. For the last 30 years, there has been a discovery gap in antibacterial drugs, with no new classes of antibacterials released to the market until 2000, when linezolid, an oxazolidinone, was approved. Inevitably, the advent of antibiotics coincided with the emergence of the phenomena of antimicrobial resistance. Based on his early results, Fleming, in 1954 predicted that indiscriminate application of this discovery would result in the selection and development of antibiotic-resistant bacterium mutants. Indeed, after only a few years of the golden age of antimicrobials, frightening signs of resistance were noticed (1).

1.1 Understanding the antibiotic resistance

The term "resistance" is a natural biological process whereby bacteria evolve and acquire genetic mutations or exchange resistance genes, enabling them to withstand the effects of antibiotics. The timeline of antibiotic resistance are depicted in Figure 1. Resistance can be divided into two groups: intrinsic or acquired resistance. Some bacterial species are innately resistant to a specific antibiotic class. Acquired resistance occurs when just select strains of a particular species are resistant to an antibiotic, rather than the entire species. This resistance can occur as a result of a spontaneous mutation in the chromosomal DNA or as an extra-chromosomal event, such as when bacteria exchange plasmids or transposons (2). There is surge in AMR, which is frequently directed towards multidrug resistance (MDR). MDR infections are difficult to treat with conventional medications. As per some studies, it is anticipated that more patients may die from MDR pathogen infections (10 million/year) than from cancer (8.2

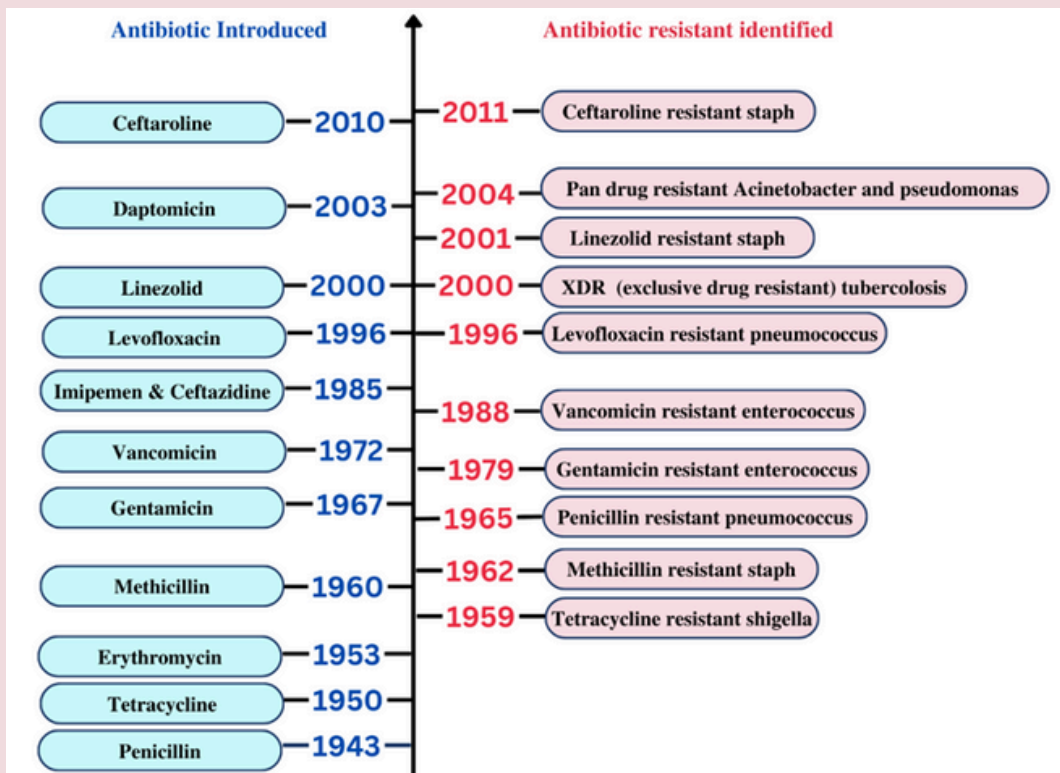


Figure 1: Antibiotic discovery and resistance timeline

million/year) by 2050 (3). Some of the most prevalent resistance mechanisms include antibiotic modification/inactivation, changes in the permeability of the external membrane, the formation of efflux pumps, and changes in the bacterial target site (4).

1.2 Causes of antibiotic resistance

The primary cause of AMR is thought to be the growing usage of antibiotics during the previous few decades. The second reason is that most patients are unable to effectively follow therapy directions. The third reason is that there are very few new medications in development within a specific class of antimicrobials to substitute those become ineffective by growing drug resistance. The use of antibiotics in agriculture to improve crop quality and yield is requisite to meet the increased demand for food and in animal husbandry to prevent infections. The use of antibiotics in agriculture contributes to the spread of resistant bacteria in the food chain and are transferred to human through direct or indirect consumption (5).

1.3 Mechanisms of antibiotic resistance

The bacteria become resistant to antibiotics through the four mechanisms (6) depicted in Figure 2.

1.4 Consequences of Antibiotic Resistance

The antibiotic resistance results in increased morbidity and mortality as resistant infections are harder to treat, leading to prolonged illnesses. Common medical procedures, such as surgeries and cancer treatments, rely heavily on effective antibiotics to prevent and treat infections. The rise of antibiotic resistance threatens the success of these procedures (6).

1.5 Approaches for overcoming antibiotic resistance

1.5.1 Discovery of new antibiotics

The most significant roadblock to novel antibiotic research is the lengthy medication production process and high cost. The current position indicates that selecting and using a new molecule identified in the laboratory would take around 15 years. As a result, instead of inventing new medications or antibiotics, researchers attempt to tweak or rediscover old ones through the various approaches, which include semi-synthetic engineering, genome mining, retro-biosynthetic algorithm and hit compounds technique (7).

1.5.2 Antibiotics adjuvants

Antibiotic adjuvants are employed not just to prevent resistance, but also to boost the efficacy of currently available medications. The majority of antibiotic adjuvants are utilised in combination therapy. Adjuvant treatments demonstrated response by (i) modifying active transport, (ii) improving drug absorption, (iii) altering drug transformation to the intestine or liver, (iv) enhancing immunological activity, and (v) decreasing excretion rate. To treat enterococcal infections, aminoglycoside and penicillin both, work significantly better than a single medicine because synergistic interactions are reached, and drug efficacy appears to be higher in this scenario rather than a single drug. As a result, germs are killed more quickly, and resistance is also inhibited (7).

1.5.3 Phytochemicals

Many infections can be efficiently treated using a combination therapy that includes botanical and nutritional approaches, such as phytochemicals, flavonoids, isoflavonoids, and many other phenolic compounds. The plant extract can also be employed as a powerful strategy to fight microbe resistance development mechanisms. Pathogens are unable to easily train resistance against phytochemical complexes derived from various plant extracts; thus, these can be employed as an alternative to antibiotics. It may include disruption of the cell membrane or increasing membrane permeability and enhancing the influx system, blockage of genome synthesis, changes in the structure of adhesion proteins and membrane-bound enzymes, and interference with cellular processes such as cytoplasm coagulation and QS inhibition. One example is guava leaf extract, which has a bactericidal effect and is also implicated in the neutralisation of pathogen-produced toxins (8).

1.5.4 Nanoparticles

In the fight against AMR, NPs perform two functions. Firstly they have bactericidal activity and the second is that they act as nanocarriers for antibiotics and AMPs. Gold nanoparticles (AuNPs) with functionalized monolayer protection have been shown to suppress clinical MDR, both against Gram-positive and G-negative bacteria. Antibiotics are conjugated or infused by cooperative or non-covalent contact with NPs in the second situation, in which they act as nanocarriers. Antibiotic efficiency is increased by this approach, resulting in high efficacy at a lower minimal inhibitory concentration when compared to free antibiotic. When vancomycin and ampicillin were combined with AuNPs, they provided effective results at low MIC against Gram-positive and G-negative bacteria, respectively (9).

1.5.5 Probiotics

Integrating antibiotics and probiotics has been demonstrated to reduce the severity, length, and occurrence of antibiotic-associated diarrhoea. This encourages patients to closely follow

Figure 2: Strategic approaches used in Bone targeting

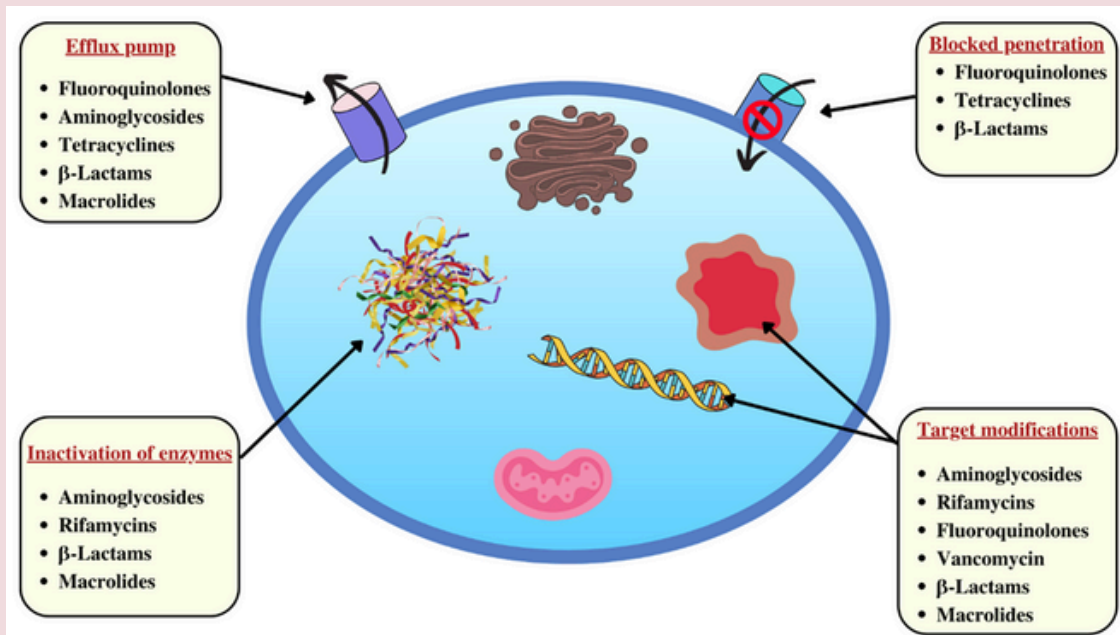


Figure 2: Mechanisms of antibiotic mechanism

their antibiotic prescriptions, slowing the spread of resistance. The extent to which probiotics directly reduce antibiotic resistance propagation is still being explored (10).

1.5.6 Bacteriophage therapy

Bacteriophage therapy involves the use of viruses called bacteriophages to target and destroy specific bacteria. These viruses are highly specific to their host bacteria, leaving other beneficial bacteria unharmed. Bacteriophages can be adapted quickly to target antibiotic-resistant strains. Research in this area shows promise in treating infections that no longer respond to traditional antibiotics (8).

1.5.7 CRISPR-Cas9 Technology

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and the CRISPR-associated protein 9 (Cas9) system have revolutionized gene editing and present a potential solution to antibiotic resistance. Scientists are exploring CRISPR-Cas9 technology to directly target antibiotic resistance genes in bacteria, making them susceptible to antibiotics again. This gene-editing approach could play a crucial role in preventing the spread of resistance genes among bacterial populations (8).

1.5.8 Stewardship Programs

Antibiotic stewardship programs aim to promote the responsible use of antibiotics in healthcare settings. These programs involve strict guidelines for prescribing antibiotics, encouraging healthcare professionals to use these medications judiciously. By reducing unnecessary antibiotic prescriptions, the development and spread of antibiotic-resistant bacteria can be curbed (8).

2. Conclusion

Antibiotic resistance is a pressing global health crisis that demands immediate and collaborative action. To overcome this challenge, a multi-pronged approach is essential, involving antibiotic stewardship, the development of novel antibiotics, exploration of alternative treatments like AMPs and bacteriophage therapy, and the integration of cutting-edge technologies like CRISPR-Cas9. It is crucial for healthcare professionals, policymakers,

researchers, and the general public to work together to ensure the responsible use of antibiotics and the implementation of strategies to preserve the efficacy of these life-saving medications for future generations.

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