Mechanistic Approaches for Combating against Antibiotic Resistance

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1.Introduction

The discovery of antibiotics was one of the milestones in human history since it revolutionized the world of medicine in many ways and helped save innumerable lives. Fundamentally, antibiotics are from natural origin; a deep understanding of the chemical structure, biosynthetic routes, evolution, and mode of action of the many antibiotic compounds is however, required. Due to its complex structure with respect to the functional groups and chiral nature, it is challenging to perform the total synthesis of these compounds in the lab. During the history of antibiotics, research on modes of action has offered biochemical knowledge on these ligands and their microbial targets (1, 2).

The wider applications and the low-cost availability have offered them a non-prescription and off-label medication status in certain parts of the world. Years of continuous choice burden from human usage of antibiotic compounds, especially the underuse, overuse, and misuse, have developed the antibiotic-resistant microbial species and dispersed them in the microbial populations through the environment. This developed resistance may not be a natural process; it might be a man-made situation, which can be a finer illustration of the Darwinian concepts of selection and survival.

2.Antibiotic resistance (AR): causes and implications

The resistance of microorganisms towards the antibiotics is of two types, acquired and intrinsic. This involves the degradation or covalent transformation of key functional groups by the bacterial enzymes causing the antibiotic deactivation. The modifications include hydrolysis, glycosylation, phosphorylation, acetylation, monooxygenation, and nucleotidylation. In few cases, the modification of the bacterial target is such that the antibiotic does not bind to the target or avoids the target by utilizing an alternate pathway for producing a molecule that is crucial for the survival of bacteria. Another mechanism is the use of the efflux protein of the bacteria to actively detoxify the antibiotic from the organism. Some organisms can alter the membrane permeability, which can affect the antibiotic entry into the organism. All or some of these mechanisms are associated with acquired mutations and genetic modifications upon prolonged exposure to the respective antibiotics class. Intrinsic resistance implies the presence of certain genes in microbial genomes that possibly will trigger a phenotypic resistance, i.e., proto- or quasi-resistance (3, 4). Different genus, species, or subspecies, etc., demonstrate different types of AR phenotypes (5, 6). Super resistant bacteria have developed a higher virulence and transmissibility in certain contexts. AR is, in reality, a pathogenicity factor (7).

3.Approaches to combat the AR

Researchers are continuously striving to combat the AR by studying several approaches but very few were successful in meeting their expectations. It is still a challenging task with the ever-increasing resistance. In this article, some important approaches have been discussed briefly.

3.1. Preventive measures

As a preventive measure, the major remedies proposed for combating AR include: strictly controlling the use of antibiotics, avoiding unnecessary prescribing of antibiotics, and building awareness among the public. However, these strategies can't control the global threat of AR that is continuously increasing due to the unrest in health conditions (2).

3.2.Antibiotic hybrids

Due to the ever-increasing resistance against antibiotics pertaining to overexpressed efflux pumps, a constant search for new strategies continues. Antibiotic hybrids are one such approach, where two or more antibiotics or an antibiotic with an adjuvant (e.g., an inhibitor of an efflux pump) are developed to target the bacteria. Antibiotic hybrids include covalently linked synthetic constructs of the two molecules. They offer the advantage of decreased risk of developing resistance, improved therapeutic effect due to additive effects of drug mechanisms thereby lowering the mortality. However, more clinical evaluations need to be conducted to confirm such advantages (8).

Li et al., has reviewed the role of supramolecular materials as a remedy to combat AR. In addition to the loading of antibiotics, the supramolecular materials also show a unique way of interacting non-covalently with biomolecules. Bioconjugated nanoparticles with penicillin G and squalene showed a different intracellular diffusion compared with penicillin G where clathrin-dependent endocytosis was observed in a neutral environment. It indicated that supramolecular-assembled bioconjugated nanoparticles have an improved activity.

Another such example for supramolecular functional materials includes beta-cyclodextrin with doxycycline, which showed an enhanced activity and a low value of minimum inhibitory concentration against S. aureus. Other examples of supramolecular materials include the application of cationic polymers, chitosan, antibacterial peptides, and metals (9).

3.3. Nano-based antibiotics

Nanotechnology has been reported to be a useful approach for combating AR. Engineered nanoparticles have the ability to disrupt the cell membranes eliminating the resistant strains. Nanotechnology also helps to predict the emergence of resistance and hence the combating measures can be implemented. By knowing the mechanisms of resistance, nanotechnology has shown to be helpful in developing nanoscale carrier systems by overcoming the existing pressures. Targeted delivery of arsenal through nanocarriers is one such promising example (10).

Nanocarriers offer improved pharmacokinetic properties for the antibiotics by restoring their efficacy against drug-resistant bacteria (11). With the ever-growing advancements in the design and development of nanotherapeutics with tailorable properties, researchers are studying their applicability to combat the AR (12). As a part of the drug-metal ion complexes, Sceptrin–Au nano-aggregates were reported to combat the drug-resistant bacterial infections. It has shown superior activity, with lower side effects, against carbapenem-resistant gram-negative bacteria (13).

3.4. Omics

Systems biology employs specific bioinformatic tools and methods that can create a comprehensive representation of the mechanisms and consequences of AR, and, sequentially, enable knowing about the events at the genomic circle by examining the increasing volume of information that gets generated in molecular biology (14). The methods include genomics, proteomics, transcriptomics, and metabolomics. Integration of the whole gene sequencing allows for the quick discovery of AR-associated genes, and higher intolerant capacity in terms of bacterial resistance contributing factors and genomic epidemiology of distinct species (15, 16).

Understanding the mechanisms of antibiotics will possibly lead to the discovery of novel ways of limiting the propagation of the resistance genes. Proteomics is extensively used to advance the understanding of the key proteome of antibiotic-resistant microbial species. Many investigators have concentrated their attempts in recent times on discovering and developing protein biomarkers that correlate with sensitivity or resistance. Such developments are made feasible with the help of enhanced proteomics methods such as matrix-assisted laser desorption ionization and time-of-flight mass spectrometry (MALDI-TOF MS) (17).

Bacterial metabolic pathways play an important role in AR and might be responsible for the acquired resistance and usually undergoing modifications in the pathway to avoid the key biomarkers which are targets for the antibiotics. For instance, elevated metabolic action is required to initiate a wide range of molecular systems, including cell wall changes, mutation steadying, transportation, energy production, and efflux pump overexpression. Metabolomics allows for a global perspective of all the compounds involved in metabolism, which are in order inherently linked to the organism's phenotype. Metabolomic methods are critical for understanding the interactions between AR mechanisms and bacterial metabolism (18).

3.5. AI or ML based methods for new antibiotics

The traditional approaches to antibiotic research are time-consuming and expensive; hence, novel and more effective ways must be utilized to choose the most promising compounds with novel processes that the bacteria are unfamiliar with (19). Based on significant advances achieved in recent years, incorporation of artificial intelligence (AI) in antibiotic creation has initiated the discovery of newer antibiotics that can offer promising results. By swiftly recommending several new compounds based on algorithms produced by machine learning (ML) approaches such as neural networks (NN) or deep learning (DL), AI helps fasten the early drug discovery process, as the algorithms foresee antibiotic efficacy for each created molecule (20). Despite continual progress in the domain of ML, the advantage against the clinical environment is yet to be accomplished.

4.Future directions

With the existing knowledge and new technologies that are coming into force, researchers can focus on hybrid mode of combining several outcomes in order to combat the AR. Computer-aided drug design and development can also be taken into count for getting better remedies within reasonable screening time. In addition, nanotechnology needs to be explored for finding more alternatives for overcoming the drug resistance. DNA-based targeted therapy could also be a possible answer to overcome this drug resistance and has a scope for future exploration.

5.Conclusion

AR which is considered as a global risk, is one of the major challenges that lies in front of the healthcare professionals. If unanswered, it will certainly turn out to be a severe disaster as the existing antibiotics cannot address these resistant infections. It is becoming very hard to understand the smart behaviour of bacteria that is changing its pattern of developing drug resistance from time to time. Awareness among the public is one of the important preventive measures and that should help the researchers identify reasonable solutions for undesired drug resistance.

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