(REVIEW ARTICLE)

Short notes on molecular mechanisms behind antimicrobial drug resistance

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Abstract

Infectious disease mortality have occurred often, raising public awareness of their hazards and advancing global antibiotic research. On the other hand, higher antibiotic levels in natural ecosystems are a result of increased antibiotic demand and use. Gene mutations causing antibiotic resistance in bacterial populations were brought on by natural selection and adaption. The emergence of antibiotic-resistant bacteria was caused by the spread of antibiotic resistance genes in ecosystems, which resulted in a number of antibiotic-resistant diseases on a global scale. An overview of the history of antibiotic discovery, antibiotic use, and antibiotic resistance mechanisms is given in this review study. Bioinformatics is also used to combat antibiotic resistance. To control bacteria that no longer respond to the therapy, the creation of new medications appears to be the primary requirement today.

Keywords: Drug resistance; Antibiotic; Bioinformatics; Mutations

1. Introduction

Infectious diseases appeared as a result of technological breakthroughs in the developing scientific period. The rate of worldwide death and morbidity increased significantly as a result. In order to find precise, effective antimicrobial measures for host survival and safety, the research community held up the fight against these infections by deeply examining their molecular mechanisms, their host-pathogen interactions, and their epidemiology. Drugs are typically understood to be foreign substances or agents with certain medical characteristics. They are effective against bacterial infections, even when cancer therapies, antifungal or anti-parasitic medications, etc. The finding of The greatest medical advancement affecting human survivability was the use of antibiotics[1-2]. Sir Alexander Fleming, the creator of penicillin, cautioned of the appearance of resistant strains of Staphylococcus aureus as a result of incorrect penicillin usage, which would result in major host issues[3]. Thus, antimicrobial resistance is not a new concept. Before the start of the antibiotic era, anti-microbial resistance was recognized. The scientific community was already aware of the issue of antibiotic resistance by the 1950s.Notably, the first time methicillin was clinically utilized was in 1959, and just two years later, researchers had already discovered the first instance of methicillin-resistant Staphylococcus aureus[4]. This proved the rapid evolution of antibiotic resistance in bacteria and other microbes. The prevalence of antibiotic resistance has rapidly increased on a global scale due to the misuse and abuse of antibiotics as well as the spread of antibiotic-resistance determinants worldwide[25]. AMR, often known as antimicrobial resistance, is a growing issue for both public health and the global economy. Multidrug-resistant pathogen infections are becoming more widely documented. This situation was made worse by the pipeline for antibiotics drying up in part due to a lack of financial incentives and a malfunctioning market system[26].

Since the first antibiotic was discovered less than a century ago, antimicrobial resistance has grown to be one of the largest risks to human development and global health. Antibiotic resistance is increasing the length of many common infections' symptoms and the fatality rate. In addition, not enough new antimicrobial medications are being produced to replace those that are becoming progressively less effective. A historic gathering of world leaders at the United

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Nations (UN) General Assembly was held in September 2016 to discuss the gravity and scale of the crisis and to commit to working together to combat antimicrobial resistance. Notably, this was just the fourth occasion in UN history that a health topic was considered at the General Assembly (the others were Ebola, non communicable illnesses, and HIV).

2. Background of drug resistance

Since the time that medications were first made available for widespread use, the evolution of drug resistance has always been a serious global issue. Antimicrobial medications were developed as a result of the important role that bacteria play in the spread of disease[5]. As was earlier established, Alexander Fleming introduced penicillin as the first of its kind in 1928[6]. It was followed by a few other antibiotics such as streptomycin, tetracycline, chloramphenicol, vancomycin, macrolides, nalidixic acid, etc. because of its efficiency against Gram-positive bacteria, particularly Staphylococcus aureus. Nevertheless, various drug-resistant bacteria also started to appear in due course. Penicillinase-producing S. aureus entered society in the 1950s, which led to the slow rise and spread of multidrug-resistant S. aureus. Methicillin was created to counter the negative effects of penicillinase-producing S. aureus, but to everyone's utter surprise, methicillin-resistant Staphylococcus aureus (MRSA) defeated mankind in the UK[7-8]. According to their antibacterial spectra, distinct generations of cephems developed over time. Penicillin-resistant S. pneumoniae (PRSP) emerged in the 1970s at the same time as penicillin-intermediate S. pneumoniae (PISP) in the second half of 1967. The elevated PRSP was thought to be caused by the frequent usage of cephems. When new strains of Haemophilus influenzae emerged in the 1980s, ampicillin, which had previously been successful against those infections, failed. Through generating -lactamase, antibiotic resistance[9]. Early in the twenty-first century, the increased use of carbapenem, quinolones, and third-generation cephems raised the incidence of resistant Gonococci, MDRP-positive P. aeruginosa, and quinolone-resistant E. coli. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis is a relatively recent issue in this field. According to statistics from 2013, 5% of all cases of tuberculosis (TB) in the globe are thought to be MDR-TB, in which the bacterium is resistant to at least two of the most potent first-line anti-TB medications, isoniazid and rifampicin[10]. In addition to resistance in bacteria, cancer research is also concerned about cancer cells developing chemo-resistance.

3. General Drug Resistance Mechanism

With new diseases arising and a higher tolerance level that contributes to mortality and morbidity, the rapidly expanding drug resistance mechanism will come to be recognized as the hallmark of powerful bacteria living in the environment. Intrinsic and acquired modes of tolerance make up the two categories of the molecular mechanism of resistance. Intrinsic refers to a microbe's inalienable quality that has evolved over time to give it resistant traits[11]. Additional genetic modifications for resistance emergence are formed by the process of mutations and selective characterization. The pathogen's genetic makeup can vary as a result of gene transfer techniques, changes to stress-regulating genes that alter protein expression, and gene amplification.

3.1. Intrinsic Resistance

The ability of an organism to resist antimicrobial/chemical agents employing a distinctive trait, which is an inherent or integral attribute developed by virtue of evolution, is referred to as intrinsic resistance. Due to the organism's immunity to that specific medicine, this is also referred to as "insensitivity". Despite being less common, the natural resistance trait occasionally experiences spontaneous genomic changes as a result of the lack of antibiotic-based selective pressure. However, the micro-ecological pressure based on antibacterials is what primarily stimulates the stimulus for pathogen adaptability through the development of drug resistance. Uptake of the drug resistance gene is enabled by mutations or evolutionary competition. It can arise due to certain events as outlined in Fig. 1
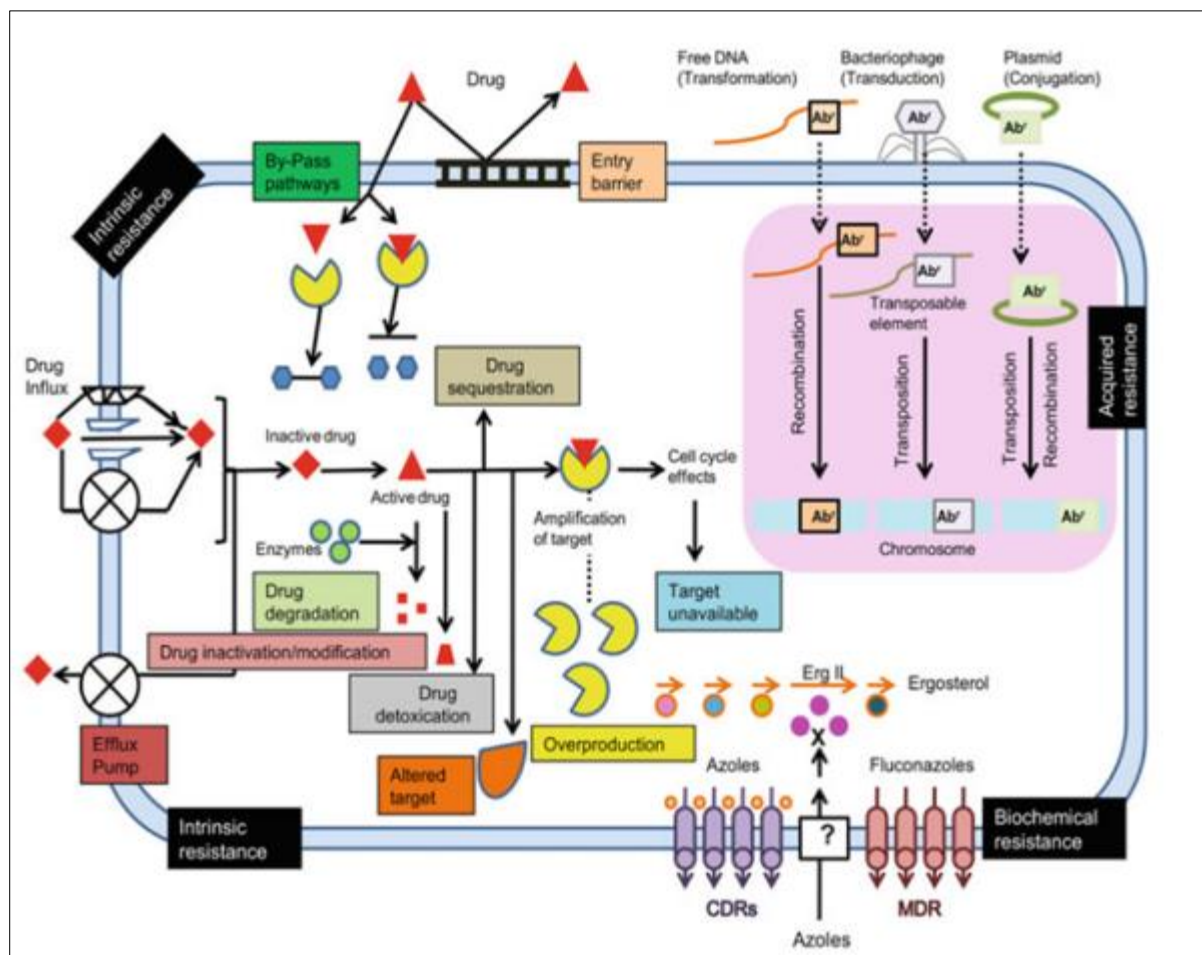
Figure 1 Multiple, varied molecular mechanisms of microbial resistance are presented schematically. (source: google)

3.2. Acquired Resistance

The organization of their genetic material that develops tolerance and the simplicity with which exogenous DNA can be incorporated to change the genetic makeup of the microbes are both factors in the development of drug resistance. As a result of the ongoing selective pressure, novel ways for pathogens to survive harsh treatments have emerged. Most often, two types of pathogens—the susceptible group and the heterogeneous group with at least one microorganism with a drug-resistant determinant—are involved in the emergence of resistance. The resistant group reemerges with updated genetic makeup coding for the resistance, aiding in its spread even further.

Following the transfer of the resistance gene, the drug treatment is altered by gene overexpression or mechanistic biological activity in a way that cancels out the effects of the drug. The medicinal agent is typically chemically or enzymatically degraded or altered by the biological process of resistance, leaving it ineffective against the insect. In the case of -lactam antibiotics, this is how resistance develops. Second, more stronger than influx modes, active drug efflux mechanisms encourage the establishment of effective resistance. Tetracycline and fluoroquinolones showed evidence of the efflux method of microbial tolerance. Thirdly, target modification entails the microorganism changing the drug's substrate binding affinity in order to reduce activity. Similar mechanisms include DNA gyrase regulation that results in fluoroquinolone tolerance and structural conformational changes in PBPs that result in penicillin resistance[12]. Acquired resistance can be developed through mutations, efflux systems, gene amplifications, pharmacological modification, or target changes.

4. Molecular Mechanisms of Antimicrobial Resistance

Numerous molecular pathways of resistance have been discovered through the genetic characterization of antibiotic-resistant bacterial strains. The five primary mechanisms of antibiotic resistance are

- Enzymatic activity, which directly inactivates or degrades the antibiotic,
- Modification of bacterial proteins, which are targets of antibiotics,
- Reduction in membrane permeability to antibiotics,
- Activation of efflux pumps, which pump out antibiotics, and
- Activation of resistant bacterial metabolic pathways.

Antibiotics are resistant to action because bacteria can destroy or change them. One important mechanism of antibiotic resistance is the inactivation of drugs by hydrolysis. Antibioticscanalsobeinactivatedbytransferofchemicalgroup. As a result of steric hindrance, bacterial enzymes add chemical groups to the antibiotic's susceptible spots on the molecule, preventing the antibiotic from attaching to its target protein. A wide range of various chemical groups, such as acyl, phosphate, nucleotidyl, and ribitoyl groups, can be transferred, as well as the enzymes that make up a huge and diversified family of antibiotic-resistance enzymes.

Another efficient method of antibiotic resistance is modification of the target bacterial protein. The majority of antibiotics bind to their respective protein targets with great affinity, stopping the proteins from acting normally. Changes to the protein structure that hinder effective antibiotic binding but still allow the protein to function normally can confer antibiotic resistance.

Most antibiotics target intracellular processes and require bacterial cell wall penetration to be effective. Gram-negative bacteria are innately less permeable to many antibiotics than Gram-positive bacteria because of their outer membrane, which acts as a permeability barrier. Antibiotics can enter the outer membrane primarily through two pathways: a lipid-mediated mechanism for hydrophobic antibiotics and a general diffusion pathway for hydrophilic antibiotics. Antibiotic sensitivity of bacteria is strongly influenced by the lipid and protein composition of the outer membrane, and drug resistance involving changes of these macromolecules is widespread. The two basic porin-based pathways for resistance to antibiotics are (1) reduction of porins or replacement of one or two key porins by another, and (2) changed function as a result of particular mutations that decrease permeability.

Generally speaking, the mechanisms underlying drug resistance in pathogenic fungi like Candida, Aspergillus, and Cryptococcus are the same as those underlying antibiotic resistance in bacteria. Reduced drug accumulation in fungal cells involves increased production of efflux pumps as well as facilitated diffusion pathways without the need for pH or ATP. Fungi typically have efflux pumps that are members of the ABC superfamily and the MFS family. Additionally, changes in drug target genes may cause structural changes in the targets' fungal proteins, decreasing the affinity of the inhibitors for their intended target. For instance, mutations in ERG11 (found in Candida albicans and Cryptococcus neoformans) or cyp51 (found in Aspergillus fumigatus), which code for the enzyme responsible for producing ergosterol, alter the enzyme's structure and reduce its affinity for some antifungal medications[13]. The inhibition of ergosterol biosynthesis limits the production of ergosterol, a distinctive component of fungal cell membranes, activating the resistance mechanism. Another strategy used in resistant fungal strains is drug target overexpression. Antifungal resistance can also be activated through stress response pathway regulation. As an illustration, the molecular chaperone Hsp90 stabilizes the regulators of cellular stress responses. Hsp90 and other pathway components, such as calcineurin and the PKC1 signalling, are over expressed in response to drug inhibition[14].
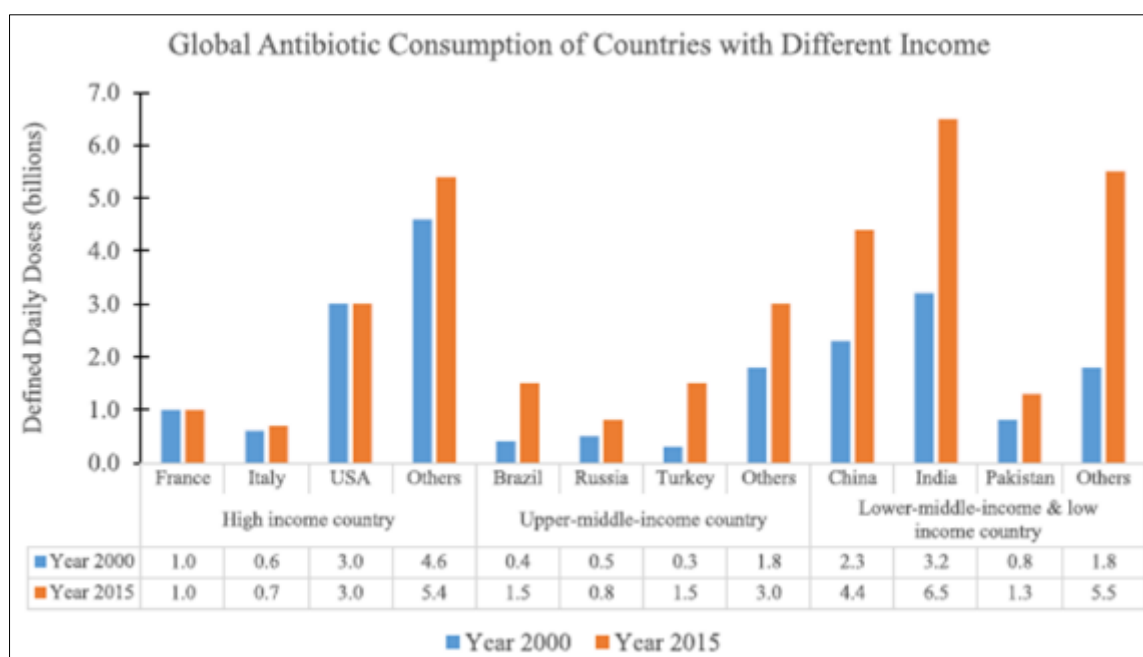
Resistance to drugs also appears in the treatment of human disorders that are not infectious. Cancer cell drug resistance might also be seen. In addition to their involvement in reducing antimicrobial resistance, efflux pumps in cancer cells also work to stop the buildup of chemotherapeutic medicines in these cells. This frequently involves the ABC superfamily's efflux pump proteins, including as P-glycoprotein (P-gp), Multi drug resistance Protein 1, Breast Cancer Resistance Protein, and Lung Resistance-Related Protein. Anticancer medications may also become inactive due to the glutathione S-transferase enzyme's ability to catalyze the conjugation of glutathione to a xenobiotic molecule by establishing a thio ether bond. Drug-resistant cancer cells can also undergo changes in their drug targets. Unlike normal cells, breast cancer resistant tumour cells lacking strogen receptors do not require strogen for proliferation. This leads to resistance to endocrine therapy. When compared to normal cells, cancer cells exhibit lower levels of membrane permeability to chemotherapeutic medicines due to the presence of high quantities of cholesterol and variations in lipid composition.

Along with the previously described generic mechanisms, cancer cells have also created unique drug resistance mechanisms. Changes in the cell cycle may alter the ratio of apoptosis to cell cycle arrest, and disruption of cell cycle checkpoints may result in drug resistance. Cells can survive a pharmacological treatment thanks to the activation of DNA damage checkpoint components. Cancer cells that are resistant to drugs may potentially avoid apoptosis by promoting cell growth. Cancer cells lack tumour suppressors that are present in healthy cells, such as p53 and the phosphatase and tensin homolog lost on chromosome 10. As a result, DNA damage repairs and cell cycle arrests are

prevented in cancer cells. A deficiency in tumour suppressors may not be the only factor preventing apoptosis; overexpression of oncogenes such the Bcl-2 gene may also play a role[15]. The most common methods for identifying antimicrobial chemicals in extracts are liquid and gas chromatography-mass spectrometry (GCMS and LCMS, respectively). By comparing the peak heights and mass-to-charge ratios (m/z) of compounds produced by mass spectrometers to values in the literature, the National Institute of Standards and Technology online database, and the WILEY library, compounds are identified in both GCMS and LCMS. Small and volatile molecules are typically detected using GCMS, however complex mixtures can be identified using LCMS thanks to its increased specificity and capacity to separate substances[16].

5. Global antibiotic consumption

The maturation of antibiotic development and the persistent occurrence of infectious diseases have recently increased the global use of antibiotics. Klein et al. (2018) claim that global consumption increased by 65% from 2.11 billion prescribed daily doses of antibiotics. (DDDs) in the year 2000 to 34.8 billion (DDDs) in the year 2015, mostly in developing nations. India's use of antibiotics, for instance dosages of DDD were increased from 3.2 billion to 6.5 billion[17].

	France	Italy	USA	Others	Brazil	Russia	Turkey	Others	China	India	Pakistan	Others
Year 2000	1.0	0.6	3.0	4.6	0.4	0.5	0.3	1.8	2.3	3.2	0.8	1.8
Year 2015	1.0	0.7	3.0	5.4	1.5	0.8	1.5	3.0	4.4	6.5	1.3	5.5

Figure 2 Global antibiotic consumption of countries with different incomes[17]

6. Bioinformatics in Combating Antimicrobial Resistance

Genomes are made more diverse by mutations, which promotes selection change and propels evolution. Drug resistance has been strongly linked to nonsynonymous single-nucleotide polymorphisms in the protein coding areas of the genome in particular. Rapid whole-microbial genome sequencing in clinical microbiology laboratories is now more feasible thanks to next-generation sequencing technologies that have reduced the cost of sequencing whole-microbial genomes and metagenomes. Furthermore, as more and more genomes are sequenced in a short period of time, the number of microbial genomes and metagenomes deposited in the NCBI Gene Bank database has grown dramatically. However, the dearth of automated, user-friendly bioinformatics tools that enable scientists and clinicians to analyze sequence data and give clinically useful information is a hurdle to the general application of whole-genome sequencing.

The Pathosystems Resource Integration Centre (PATRIC) team has also created new tools to aid researchers in understanding the genetic basis of drug resistance in response to growing concerns about antimicrobial resistance[18]. The team developed machine learning-based classifiers that can predict antimicrobial resistance phenotypes and the genomic regions associated with drug resistance that can be used for comparative analysis using antimicrobial resistance phenotype data from more than 15,000 genomes in the PATRIC database. Additionally, drug resistance databases have been created for particular species like HIV and Mycobacterium tuberculosis. However, the majority of

studies on bacterial antibiotic resistance did not explore how various genetic changes and gene-gene interactions contributed to the establishment of transmissible drug resistance. Recently, a team of scientists from Huazhong Agricultural University (Wuhan, China) used GBOOST, a program for locating gene-gene interactions in genome-wide association studies, to uncover gene pairs linked to Mycobacterium tuberculosis treatment resistance[19]. A chi-square test approach was utilized to look at the interaction effect between two SNPs and phenotypes, and GBOOST was used to find SNP-SNP interactions on the risk of drug resistance. The processes driving drug resistance in different bacteria can be better understood using this technique.

Currently, high-throughput screening (HTS) is frequently employed in drug discovery to screen sizable natural and synthetic chemical libraries against particular protein targets. Even with the utilization of robotics, this process can be costly and time-consuming. When used to supplement the HTS method in drug development, computer-assisted or virtual screening (VS) can assist in overcoming some of the drawbacks of a full HTS. In the latter, VS is used to narrow down a large library's possible active chemicals before moving on to the more expensive and time-consuming HTS trials. VS simulations do not necessitate the physical production of chemicals, in contrast to HTS experiments. VS still needs experimental data, such as protein structure for a structure-based method or the binding characteristics of substances that are known to be active for a ligand-based approach. Due in significant part to the effectiveness of these computations, molecular docking approach is frequently utilised in VS simulations. Molecular docking, as compared to lab testing, often only requires a few minutes of computation time on a single core per ligand; as a result, 10,000 to 100,000 compounds can be virtually screened on a small- to medium-sized cluster in a day. While the structure-based VS is predicated on molecular docking, the ligand-based approach is based on the similarity principle, which holds that comparable substances would likely have similar biological effects. With this method, huge ligand libraries can be screened for substances that share the same chemical characteristics as the recognized actives, leading to the discovery of new potentially active substances.

7. Treatments

The human ABCB1 gene produces MDR1(p-glycoprotein), a crucial drug transporter at the cellular level. Drug resistance rises when MDR1 is overexpressed. As a result, ABCB1 levels can be reduced. Metformin is an example of a secondary treatment that has been successfully utilised in conjunction with primary pharmacological therapy in patients with high levels of ABCB1 expression[20]. Drugs made to prevent the processes of bacterial antibiotic resistance are used to treat antibiotic resistance, an issue that is increasingly prevalent nowadays. For instance, the use of antibiotics like nafcillin, which are resistant to being destroyed by specific beta-lactamases (the group of enzymes responsible for breaking down beta-lactams), can be used to overcome bacterial resistance against beta-lactam antibiotics (such as penicillin and cephalosporins)[21]. In order to prevent the antibiotics from being destroyed by the bacteria before they can do their job, beta-lactam bacterial resistance can also be treated by combining beta-lactam antibiotics with medications that block beta-lactamases, such as clavulanic acid. The need for new antibiotics that block bacterial efflux pumps, which move molecules of various antibiotics like beta-lactams, quinolones, chloramphenicol, and trimethoprim out of the bacterial cell to produce resistance, has recently been recognized by researchers[22-23]. Destruction of the resistant bacteria can also be achieved by phage therapy, in which a specific bacteriophage (virus that kills bacteria) is used[24].

8. Integral efforts are required

It will take a lot of work to keep the terrible forecast from coming true. Increased awareness of the dangers of antibiotic overuse, better surveillance, optimizing the length of antibiotic treatment, a potential change in prescribing methods, novel antibacterial compounds, and educating more stakeholders are required. Tracing the origins of antibiotic resistance, including but not limited to antibiotic resistant bacteria (ARB), antibiotic resistance genes (ARGs), non-genetic mechanisms of antibiotic response modulation, and communication are also necessary[27]. Indole, indole acetic acid, polyamines, ammonia, cyclic diguanylate (c-di-GMP), cAMP, 13-methyltetradecanoic acid, and the Pseudomonas quinolone signal are examples of metabolic byproducts that can act as information chemicals and modulate bacterial responses to antibiotics, altering intrinsic resistance to antibiotics and its spread among bacterial cell populations. Additional research into these metabolic byproducts can help identify new antibiotic targets, particularly the important molecular cues that are influencing the rise in intrinsic antibiotic resistance[28-30]. One health-based approaches are essential to combating antibiotic resistance because they take into account antibiotics used in both human and veterinary medicine, livestock growth promoters that spread highly mobile ARG across the environment, clinical and animal-associated bacteria, and microbial ecology, such as phage-mediated ARG transfer. This is essential for informing sustainable development policies. Effective and timely communication of the issue of resistance is crucial to addressing antibiotic resistance as well[31-32].

Integrated multi-omics studies to better understand the complex mechanisms of action of current antibiotics, cost-effective techniques to effectively monitor the distribution, spatiotemporal dynamics of antibiotic resistance genes, their proliferation, dissemination, and influencing factors in environmental ecosystems, are just a few areas where future primary research should concentrate. Cross-section studies are urgently required to identify these gaps. The most desirable new technologies, especially when portable, include high-throughput sequencing, which can simultaneously sequence thousands of antibiotic-resistant gene targets representing a full spectrum of antibiotic resistance classes. This can help to overcome some of the challenges affecting the antibiotics resistance survey.

The selection pressure for antibiotic resistance and cross-resistance can be increased when microorganisms are repeatedly exposed to substances other than antibiotics. One such chemical is triclosan, a biocide that is frequently used in cleaning products for the home and body to limit microbial development and a developing contaminant. In genes that code for bacterial efflux pumps and fatty acid production, the triclosan can choose and enhance mutations that can expel antibiotics and impart broad-spectrum tolerance to them. Provisional management during the pandemic phase will help to prevent more serious development and dissemination of different resistance genes[33]. DNA adenine methyltransferase (dam), which is involved in replication, mismatch repair, and transposition, is an epigenetic component that helps protect against antibiotic stress. More in-depth research in this poorly defined area may lead to new mechanistic knowledge regarding antibiotic resistance and hasten the identification of new antibiotic targets. Lysine 2-hydroxyisobutyrylation (Khib), a protein post translational modification conserved in eukaryotes and prokaryotes, is a novel mechanism linked to antibiotic resistance that is relatively new to this field[34]. For bacterial social adaptation, virulence factor synthesis, biofilm formation, and antibiotic resistance, quorum sensing (QS) is a key regulatory and cell-to-cell communication system. Numerous metabolites participate in QS. One of those being researched extensively is indole. Indole controls various aspects of bacterial physiology by acting as a signalling molecule between cells, between species, and across kingdoms. Additionally, indole controls several bacterial phenotypes necessary for resistance to antibiotics. The potential of quorum sensing inhibitors (QSIs), which can be employed alone or in combination with conventional antibiotics, is investigated. A desirable method for combating antibiotic resistance is the creation of novel antibiotic adjuvants[35].

9. Increased international attention

The Global Action Plan on Antimicrobial Resistance (GAP-AMR) was adopted by WHO in 2015. The strategy relies on a holistic approach, which calls for coordinated effort across all pertinent industries. Five strategic goals are outlined in the worldwide action plan to combat antimicrobial resistance:

- To increase knowledge of and comprehension of antimicrobial resistance;
- To strengthen knowledge through surveillance and research;
- To reduce the incidence of infections;
- To optimize the use of anti microbial agents, and
- To expand investment in innovative drugs, diagnostic tools, vaccines, and other interventions while developing the economic rationale for sustainable investment that considers the needs of all nations.

The United Nations' Food and Agriculture Organization (FAO) and the World Health Organization (WHO) have both endorsed the GAP-AMR through resolutions[36].

In addition to the GAP-AMR, ideas for a global development and monitoring framework on antimicrobial resistance were addressed at the World Health Assembly in 2016. The goal of such a potential framework would be to create value and accomplish the strategic goals outlined in the GAP-AMR, concentrating on development of new health technologies for preventing and controlling antimicrobial resistance; preservation of antimicrobial medicines through a stewardship framework covering control, distribution, and appropriate use; and promotion of affordable access to new and existing antimicrobial medicines and diagnostic tools. While antimicrobial resistance affects all nations, each nation should take steps to address its own requirements and health system's capabilities in order to protect the world's supply of antibiotics.

10. Conclusion

One of the main issues facing modern science is drug resistance. The expected biochemical and molecular causes of resistance complexity, which have serious effects on survival, are still being studied. New chances in the clinical sector for a larger biological interest have developed as a result of study and understanding of pathogen fitness cost and tolerance dynamics. The inherent methods slow down the reversibility process. The development of new medications

is urgently needed, and there are plans in place to avoid microbial tolerance. On the other hand, by modifying the way therapeutic drugs are developed and used to treat both infectious and non-infectious diseases, such as cancers, the use of bioinformatics tools enables the practice of precision medicine, or the administration of the right medication at the right dose for the right patient at the right time, in order to address the drug resistance crisis.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest regarding this paper.

Availability of data and materials

The data and materials used to support the findings of this study are publicly available.

Author contribution

All author contributed significantly to design and development of this work.

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