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DRUG RESISTANCE: THE ALARM OF NEW CHALLENGE AND ALTERNATIVE APPROACHES

Fadia Falah Hassan[1*], Rana Alaa Al Aamery[2], Marwa Khalil Ibrahim[3]

[1,2,3]Department of Biology, College of Education for Pure science / Ibn-Alhaithum, University of Baghdad, Baghdad, Iraq.

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Corresponding Author: Fadia Falah Hassan
Department of Biology, College of Education for Pure science / Ibn-Alhaithum, University of Baghdad, Baghdad, Iraq.

ABSTRACT

The significant morbidity and mortality resulting from antimicrobial resistance in bacterial infections is a concern within the medical community. The emergence of multidrug-resistant Gram-positive and Gram-negative bacteria poses a considerable challenge in treatment, as these strains may exhibit resistance even toward conventional medications. Given the lack of efficacious treatments, preventative measures, and novel antibiotics, bacterial infections and their associated diseases present formidable obstacles that necessitate the exploration and development of innovative therapeutic alternatives and alternative antimicrobial agents. Multi-drug resistance is linked to biofilms, which can make infection control difficult. Having enough information and understanding may be the key to controlling MDR. The monitoring of the use of antibiotics and other associated issues requires strict regulatory laws and regulations on a global scale. The major threat posed by MDR must be eliminated, hence multidisciplinary approaches must be taken into consideration. In this review, we made an effort to elaborate on the key elements of antimicrobial resistance (AMR), as well as its effects, processes, regulation, associations, and control measures. The most crucial steps in managing antibiotic resistance are public awareness and education campaigns. Sustainable development aims to eradicate AMR, and we must all work together to do this. The current review focuses on the possible reasons responsible for drug resistance, therapeutic alternatives, and surveillance of the emergence of antibiotic resistance.

INTRODUCTION

Antibiotics have emerged as a valuable asset within the realms of human and animal healthcare, they are providing cutting-edge medical research on the management of bacterial infections and other illnesses. However, the development of antibiotic resistance has reached alarming proportions, owing to the emergence of novel bacterial strains, extensive antibiotic usage, and indiscriminate consumption practices. The rapid dissemination of multidrug resistance poses a significant global threat. Despite its gravity, our understanding of drug resistance, regulation, and control mechanisms still needs to be improved. Therefore, there is an urgent need for comprehensive investigations into the molecular

analysis of resistance genes, their distribution patterns, and underlying mechanisms. This research endeavor is crucial to decipher the origins and implications of antibiotic resistance.

Antibiotic resistance is not just a significant problem; it is also one of the top ten global public health issues that are flourishing globally. Antimicrobials are frequently referred to as antibiotics, antiviral, antifungal, and antiparasitic. The situation involving resistance's negative impacts is far more extensive than people realize. Over many decades, a variety of antimicrobials have been developed and distributed with a common objective of treating and curing mild to severe infections. Due to the accidental discovery of penicillin in the late 1920s, numerous improvements to the revolutionary antibiotic penicillin itself were also made. New anti-viral medications have also been developed as a result of research for the treatment of diseases that were previously incurable, such as AIDS and other disorders.[1]

The rise of the phenomenon of antimicrobial resistance (AMR) in response to antimicrobials has significantly reduced the utility of these antimicrobials, despite the important role they have played in enhancing our health and life expectancy. The main effect of AMR is to make infections more challenging to treat and greatly raise the risk of disease transmission, life-threatening illness, and death as antimicrobials lose their effectiveness.[2] AMR is notable for its diversity in size and shape. Numerous organisms are becoming more and more multi-drug resistant (MDR), making treatment even more difficult. However, organisms that are extensively drug-resistant (XDR) and pan-resistant (PDR), which are practically impossible to treat with conventional medicines, are of the highest priority.[2,3]

According to the 2019 report from the World Health Organization (WHO), antimicrobial resistance (AMR) has been responsible for the loss of 700,000 lives, and projections indicate that this number could escalate to a staggering 20 million by 2050, with associated costs exceeding $2.9 trillion.[4] Consequently, AMR has emerged as a pressing issue that poses substantial threats to both our economy and our way of life. Moreover, the escalating pace of AMR evolution, coupled with the high costs associated with antibiotic development, has significantly diminished the investment returns for the pharmaceutical research and development (R&D) sector. Consequently, many pharmaceutical corporations have abandoned their efforts in researching and developing new antibiotics.[5] Despite this dire situation, there exist several emerging technologies with the potential to ameliorate these circumstances. Numerous scientific advancements hold promise in supporting the discovery and development of innovative antibiotics.

Synthetic biology techniques seek to identify the planet's natural products more quickly than antibiotic discovery through genetic, functional genomic, and metagenomics research of bacteria, mammals, and even aquatic invertebrates.[6] Bacteriophages[7], monoclonal antibodies[8], and vaccinations[9] are a few examples of the various therapeutic and preventative techniques used to treat and prevent bacterial diseases. Innovative methods like the "Defence Advanced Research Projects Agency bionic spleen" offer a potential therapeutic substitute.[10]

Early antibiotic era

The initial milestone in the antibiotic discovery field can be attributed to the extraction of Mycophenolic acid from P. glaucum, a significant achievement made by the renowned Italian microbiologist Bartolomeo Gosio in 1893. This seminal discovery unveiled the inhibitory effects of Mycophenolic acid against the growth of Bacillus anthracis.[11] Subsequently, another notable breakthrough occurred in 1909 with the pioneering work of Paul Ehrlich and his colleagues, who successfully synthesized Salvarsan (arsphenamine), marking the first synthetic antibiotic derived from arsenic. Salvarsan showcased remarkable effectiveness in combating Treponema pallidum, a causative agent of

syphilis.[12] In 1928, a fortuitous discovery was made by the Scottish bacteriologist Alexander Fleming, who observed the inhibitory effect of a fungus called Penicillium notatum on the growth of Staphylococcus aureus colonies. Subsequently, in 1929, Fleming successfully isolated the active molecule responsible for this antibacterial activity and bestowed upon it the name "penicillin," thus marking its distinction as the first bona fide antibiotic. Fleming hypothesized that the fungus had released a substance capable of inhibiting the growth of bacteria. However, it was through the subsequent research efforts of Howard Walter Florey and Ernst Boris Chain that the structure of penicillin G—the first antibiotic employed for treating bacterial infections—was elucidated in 1939. Their work not only enabled the effective purification of the drug but also contributed to its enhanced production capabilities.[13]

A significant milestone in antibiotic research occurred with the introduction of penicillin into medicine in 1945.[14] Concurrently, Dorothy Crowfoot Hodgkin employed X-ray crystallography techniques to elucidate the molecular structure of penicillin, thereby establishing its classification as the inaugural member of the naturally occurring antibacterial-lactam family.[15] The β-lactam family encompasses penicillin, cephalosporins, monobactams, and carbapenems, all characterized by a β-lactam ring and exhibiting similar bactericidal mechanisms. These compounds collectively fall under the class of antibiotics known as β-lactams. Notably, β-lactam antibiotics exert their inhibitory effects on the synthesis of cell walls in Gram-positive bacteria.[16]

The golden period of antibiotics

In 1939, the pioneering work of the French microbiologist René Dubos contributed a significant chapter to the ongoing narrative of antibiotic development through the discovery of tyrothricin from the soil-dwelling bacterium Bacillus brevis. Tyrothricin emerged as a highly effective inhibitor of Gram-positive bacteria, consisting of gramicidin D and tyrocidine. It is worth noting, however, that gramicidin exhibited pronounced toxicity in humans, leading to its exclusive topical application at present.[17]

During the 1940s, Selman Waksman embarked on a comprehensive exploration of the antibacterial properties exhibited by soil bacteria, with particular emphasis on Streptomyces spp. Through his innovative framework known as the Waksman-framework case, Waksman successfully delineated bacterial species that displayed antagonistic interactions. Leveraging this platform, he made numerous groundbreaking discoveries, including actinomycin (derived from *Streptomyces spp*.), neomycin (derived from *Streptomyces fradiae*), streptomycin (derived from Streptomyces griseus), clavacin (derived from *Aspergillus clavatus*), and fumigacin (derived from *Aspergillus fumigatus*), all of which held significant implications in the realm of antibiotics and antifungals.[18]

Actinomycin, streptomycin, and neomycin are prominent examples of antibiotics that continue to be employed in contemporary clinical settings.[19] During the "golden age" of antibiotic discovery, a multitude of bacterial and fungal species yielded the identification of more than 20 distinct antibiotic classes.[20] This period witnessed the adoption of rational screening approaches by several pharmaceutical companies, leveraging knowledge surrounding the established mechanisms of action of antibiotics as facilitated by Waksman's culture-based platform.[21,12] Despite this era of prolific antibiotic discovery, only a limited number of novel antibiotic groups have emerged since then. Noteworthy examples include the identification of nitrofurans in 1953, macrolides in 1952, tetracyclines in 1948, quinolones in 1960, and oxazolidinones in 1987.[17,20] It is worth noting that different strains of this bacterium have the potential to carry cryptic plasmids that do not possess detectable antibiotic resistance or virulence genes. Notably, specific plasmids are employed in the creation of H. pylori-Escherichia coli shuttle vectors for cloning research.[19]

There was an overuse of antibiotics due to their rapid and relatively simple development over a short period of time. This has led to the current situation, where there aren't many novel antibiotics in clinical trials, along with a pipeline of antibiotic research that has been stagnant since the 1970s. Since the 1980s, over 1200 antimicrobial peptides (AMPs) from a variety of sources, including plants, invertebrates, and mammals, have been identified; however, none of them have proved effective as antibiotics.[22]

Current circumstances and upcoming strategies

Currently, the development of new antibiotics is constrained, as evidenced by the limited number of ongoing projects.[23] Only five of the original twenty pharmaceutical companies involved in antibiotic research during the 1980s continue to pursue this pursuit. Consequently, many major pharmaceutical companies have redirected their focus from discovering novel antibiotics, leaving smaller start-ups and biotechnology companies to shoulder the responsibility.[20] Notably, a database from 2018 reveals that among the 45 novel antibiotic candidates undergoing clinical trials for the US market, only two belong to major pharmaceutical companies, while the majority are being conducted by research laboratories and small to medium-sized enterprises.[15]

The primary cause underlying this predicament is the issue of antibiotic resistance. Although resistance to antibiotics has been observed since their early introduction, the constant influx of experimental medications offered viable alternatives, enabling easy switching of treatments in the face of emerging resistance to a particular antibiotic.[24] However, during the 1980s, the pipeline for novel antibiotics experienced a significant decline. The identification and commercialization of a new antibiotic class have not occurred since 1987, while fluoroquinolones marked the last discovery of a broad-spectrum drug class.[22] Subsequently, the field has witnessed a need for substantial innovations, resulting in the limited development of new antibiotic families capable of effectively addressing the prevailing levels of antimicrobial resistance.[25] These techniques are crucial, but their applications have some limitations, and they haven't yet been converted into medical devices. Nevertheless, they might serve as a helpful adjunct to antibiotics or another treatment. Scientists are investigating a number of novel strategies based on an updated understanding of the dynamics of resistance, disease, and prevention.

The ability to quickly identify resistance pathways and control bacterial resistance makes whole genome sequencing (WGS), one approach, a crucial method for drug discovery.[26] The recently found quorum-quenching (QQ) approach, which interacts with microbial cell-to-cell interaction to inhibit bacterial infections, is another potential strategy.[27] Bacteriophages, often referred to as viral phage treatment, have recently grown in favor due to their superior efficacy to antibiotics since they are non-toxic to the host organisms they are intended to treat, including the gut flora, reducing the risk of opportunistic infections.[28] Phages are currently being rediscovered as a possible alternative to antibiotics, having been actively utilized to treat bacterial infections even before the rise of antibiotics, particularly in Russia and Georgia.[26]

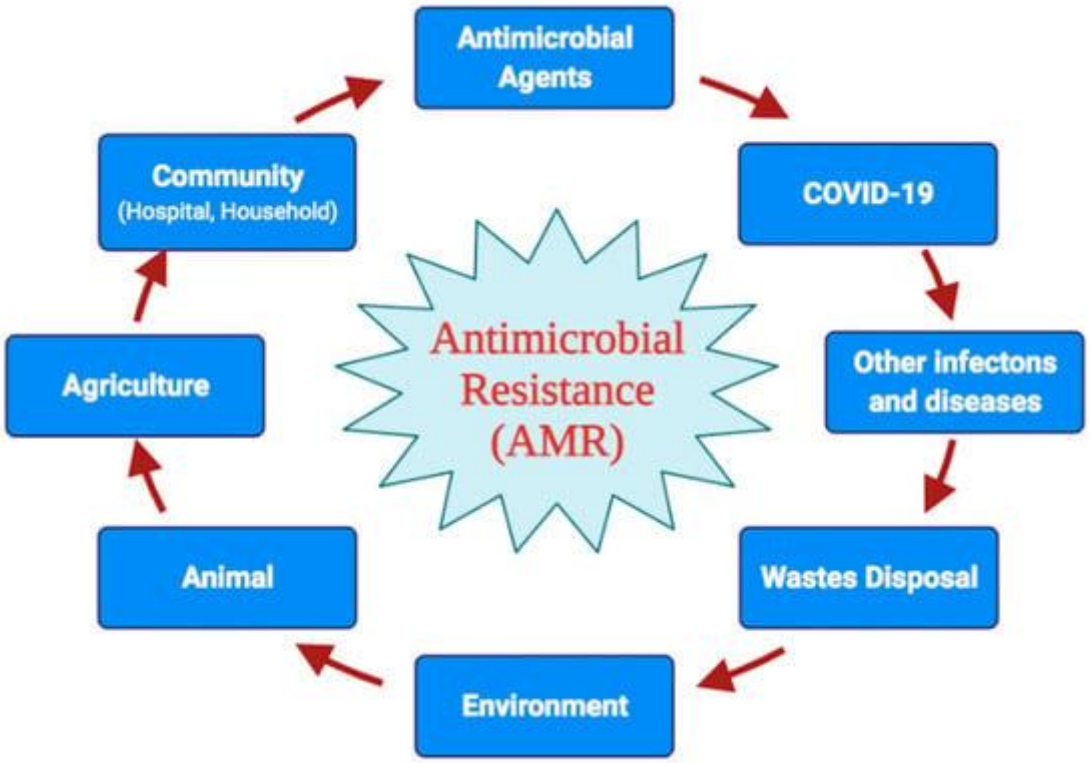

Figure 1: Schematic illustration of the many origins, contributing factors, and effects of the emergence and spread of antibiotic resistance.

Image curtesy: Saha *et.al.*

Underlying causes of antibiotic resistance

Antibiotic resistance encompasses a diverse range of mechanisms by which microorganisms can evade the effects of antimicrobial agents. Notably, resistance arising from enzymatic modification of the target has garnered growing recognition in clinical settings. This resistance strategy particularly impacts the efficacy of glycopeptides, polymyxins, and various antibiotics that target the ribosome.

Bacteria and other microorganisms are dynamic entities that undergo continual adaptation and evolution over time. Their primary objective is to proliferate, persist, and propagate rapidly. Accordingly, these microorganisms respond to environmental changes and develop strategies that enhance their survival and proliferation.

Genetic changes could occur that make the bacteria resistant to the medicine and enable them to survive if something, like an antibiotic, inhibits their capacity to proliferate.[29] Bacteria naturally develop antibiotic resistance over time. However, a number of factors are still at play in the complex etiology of antibiotic resistance at the moment. This includes overusing and abusing antibiotics, making poor diagnoses and prescriptions, losing patient sensitivity and self-medicating, creating unfavorable healthcare environments, practicing poor personal cleanliness, and using antibiotics extensively in agriculture.[30,31]

The antibiotic resistance crisis' reasons

Overuse of antibiotics: The overuse of antibiotics has been extensively studied in epidemiological research, revealing a clear and direct correlation between antibiotic consumption and the emergence and dissemination of drug-resistant

bacterial strains.[32] The persistent threat of antibiotic resistance poses significant challenges to modern medicine. Notably, pathogens have increasingly employed the strategy of altering drug targets as a means of evading antibiotic activity. This phenomenon is observed, for example, in the glycopeptide and polymyxin resistance, where chemical modifications occur in the molecular targets located within the cell membrane. Similarly, rRNA methylation compromises the effectiveness of numerous antibiotics that target ribosomes. In these instances, enzymatic alterations rather than genetic mutations are responsible for modifying the antibiotic target, with resistance enzymes swiftly disseminated among microorganisms. Effectively combating resistance necessitates a comprehensive understanding of the specific enzymes responsible for these modifications. In this article, we examine the state of our knowledge on enzymatic modification of antibiotic targets and talk about countermeasures.[33]

Antibiotic Resistance by Enzyme-Mediated Target Modification

Numerous molecular mechanisms are used by bacteria to develop resistance against antibiotics.[34] For instance, enhanced efflux (through higher efflux pump activity[35]) or decreased influx (by downregulation or porin mutation[36]) can both reduce access to the target. An antibiotic cannot bind to a target that has been altered through mutation or post-translational modification. Additionally, inside the cell, antibiotics themselves can be altered or destroyed.[37] In numerous of these processes, enzymes are essential. The hydrolases that deactivate the -lactam antibiotics, including cephalosporins, penicillins, and carbapenems, are one of the most therapeutically significant and common classes of antibiotic resistance enzymes. Kinase, acetyltransferase, and nucleotidyltransferase-catalyzed drug changes are also frequent and are notably connected to aminoglycoside antibiotics. A collection of enzymes that are increasing in clinical importance modify the molecular targets of antibiotics. Bacterial organisms can produce enzymes that facilitate the addition of chemical groups or modification of side chains at susceptible sites on antibiotic molecules. Such enzymatic actions impede the binding or attachment of antibiotics to their target proteins or sites, rendering them ineffective. Consequently, the emergence of antibiotic resistance can occur. These enzymes can transfer a variety of chemical groups, including acyl, phosphates, and nucleotides, to vulnerable locations, adding to the vast and varied family of enzymes that are resistant to antibiotics. Specifically, because of their large molecular size and lots of exposed amide and hydroxyl groups, aminoglycosides, are particularly vulnerable to modifications, resulting in elevated levels of resistance against modified antibiotics. Among the mechanisms underlying aminoglycoside resistance, three primary types of modifying enzymes have been identified: acetyltransferases, phosphotransferases, and nucleotidyltransferases. A recent study unveiled the presence of a novel genomic island within Campylobacter spp. They are isolated from broiler sources, which encodes six distinct aminoglycoside-modifying enzymes encompassing members from all three enzyme classes. This genomic island confers resistance against several aminoglycoside antibiotics.[52]

Evolution and Transmission of Resistance Genes

The microbial realm is characterized by its ancient origins, vast diversity, ubiquitous presence, and intricate nature. Bacteria, in particular, have developed a repertoire of resistance mechanisms in response to various challenges, including heavy metals, naturally occurring antibacterial compounds (e.g., beta-lactams like penicillin and carbapenems), and synthetic antimicrobials (e.g., fluoroquinolones and sulphonamides). These resistance mechanisms have arisen through a cumulative process of random mutation over countless generations of microorganisms.[38,39] Additionally, there is evidence suggesting that certain microorganisms possess the ability to horizontally transfer genes that encode resistance mechanisms for antimicrobial substances.[40]

Bacterial adaption to antibiotics

It is commonly known that bacteria can adapt to adverse environments very well. The ever-declining efficacy of antibiotic treatments clearly shows the therapeutic relevance of this trait. Bacterial strains that have developed methods to circumvent drug inhibition and lethality benefit from repeated exposure to antibiotics. The growing antibiotic resistance or tolerance of many strains, especially diseases that might cause death, greatly affects therapeutic practice. Unsettlingly, current research demonstrates that in an evolutionary context, bacterial populations' tolerance levels are exceedingly malleable in addition to resistance. Here, we review laboratory studies that shed light on how tolerance and resistance develop over time as well as how treatment settings may influence how bacteria evolve in response to antibiotic stress.[41] Antibiotic resistance represents a natural phenomenon that has evolved over billions of years, as evidenced by antibiotic resistance genes (ARGs) within microbial populations. Remarkably, even before the clinical utilization of antibiotics, environmental bacteria harbored ARGs that contributed to the emergence of resistance against newly approved antimicrobial agents.[42] Studies have demonstrated that bacteria from permafrost samples exhibit resistance mechanisms that have evolved independently of human activities.[43,44]

Intrinsic resistance can arise when certain antibiotics are unable to effectively target bacteria due to the inherent structural or functional characteristics of the microbial species. For instance, in some cases, certain antibiotics can penetrate the bacterial outer membrane and reach their intended target sites. In contrast, others encounter barriers that prevent successful entry or efficient removal through efflux mechanisms after translocation via porin channels. Intrinsic resistance is often attributed to the absence of sensitive targets for a specific antibiotic. For example, the gram-negative Pseudomonas spp. Exhibits inherent resistance to the biocide triclosan due to the fabI-insensitive gene encoding an alternative enoyl-ACP reductase enzyme that is not affected by the antibiotic, unlike its sensitive counterparts.[45]

Moreover, Gram-negative bacteria exhibit lower levels of anionic phospholipids in their plasma membranes than Gram-positive bacteria. This distinction diminishes the efficacy of Ca2+-mediated daptomycin insertion into the plasma membrane of Gram-negative bacteria, resulting in reduced susceptibility to this particular class of antibiotics.[46] Consequently, the inherent dissimilarity in membrane composition renders liposidomycin, which primarily targets Gram-positive bacteria, ineffective against Gram-negative counterparts.

In addition to inherent resistance, Bacteria can acquire antibiotic resistance by several different processes in addition to innate resistance. One such mechanism involves reducing the intracellular concentration of antibiotics by impeding bacterial osmosis or facilitating antibiotic efflux.[47] Furthermore, bacteria can modify target proteins through post-translational or genetic alterations, thereby evading the action of antibiotics. The bacterial efflux pump plays a crucial role in actively transporting antibiotics to the extracellular environment, rendering them ineffective. This serves as the primary cause for the natural resistance displayed by Gram-negative bacteria against several medications typically employed to treat Gram-positive bacterial infections. The overexpression of efflux pumps has been associated with the development of antibiotic resistance. Numerous efflux systems are present in bacteria, as evidenced by a wealth of data acquired from bacterial genomics. The coexistence of particular efflux pumps can result in multidrug resistance (MDR), greatly increasing bacterial resistance to several medications. Notably, the MexXY pump system in Pseudomonas aeruginosa has been identified as a key factor contributing to aminoglycoside antibiotic resistance.[48]

By altering the antibiotic structure

Bacteria possess various mechanisms through which they can acquire resistance to antibiotics, including enzymatic degradation, prevention of antibiotic entry into cells, and self-alteration. Enzymatic alteration represents a significant cause of antibiotic resistance, whereby numerous enzymes capable of breaking down and modifying different types of antibiotics, including -lactams, aminoglycosides, phenols, and macrolides, have been identified over years of extensive research.[49] Among these enzymes, Beta-lactamases play a crucial role in hydrolyzing Beta-lactam antibiotics, which encompass penicillins, cephalosporins, carbapenems, and monobactams.[50,51] Additionally, other enzymes are implicated in the breakdown of antibiotics within the same class.

Other mechanisms of drug resistance

Despite the comprehensive characterization of the major antibiotic resistance pathways that hold clinical significance, significant knowledge gaps persist. The processes by which ABC-F proteins impart resistance against a wide range of therapeutically significant antibiotic classes that interfere with Gram-positive bacteria's ability to synthesize proteins are one such gap. Notably, Sharkey et al. made a significant discovery regarding these antibiotic-resistant ABC-F proteins, elucidating their role in ribosomal resistance through the replacement of bound drugs within ribosomes, thereby providing ribosomal protection.[53,54] In Mycobacterium tuberculosis, mutations in RV2887 result in upregulating RV0560c expression. The pyridine benzimidazole 14 can render the S-adenosyl-l-methionine-dependent methyltransferase, RV0560C, inactive through N-methylation modification.[53,54]

Moreover, bacteria residing within biofilms often encounter limited oxygen and nutrient availability. In response to such stressful environments, bacteria exhibit metabolic pathway adaptability, leading to the development of drug resistance against a diverse range of antibiotics.[55] Studies have suggested that due to the intricate structure of exopolysaccharides, DNA, and protein-based biofilms, antibiotics face challenges in penetrating the biofilm matrix and reaching their intended bacterial targets.[55] Furthermore, antibiotics are more prone to deactivation at the biofilm surface, impeding their diffusion throughout the biofilm matrix. However, it should be noted that not all biofilms exhibit this characteristic, and the efficacy of this mechanism as a promoter of antimicrobial resistance remains uncertain.[55,56]

One of the biggest benefits of the biofilm environment is the close proximity of many organisms, whether they be bacteria or fungi. This not only permits quorum sensing and other bacterial communication techniques, but it also facilitates the transfer of mobile genetic elements. In fact, the biofilm environment promotes plasmid stability and makes it easier for organisms to communicate resistance-related information. To make matters worse, many of the transposable DNA elements that bacteria transmit encode components that promote biofilm formation, which helps the biofilm persist and the patient's disease.[56]

Alternative approaches for the management of drug resistance

As the efficacy of antibiotics diminishes due to the emergence of drug-resistant bacteria, attention must be diverted towards alternative approaches for treating infections. While natural alternatives exist, their practical application in clinical settings may need to be revised. However, advancements in synthetic chemistry, genetic engineering, and biotechnology offer new avenues for developing antibiotic replacement therapies. Alternative strategies that show promise, like lysins, probiotics, and antimicrobial peptides, are presently in different phases of development. In addition, bacteriophages and antibodies have been widely used in the fight against drug resistance.[57]

To address antimicrobial resistance, researchers are exploring plant-derived substances (PDS) as potential alternatives or adjuncts to antibiotics. The diverse metabolic, genetic, and physiological properties of plants, the rapid evolution of resistant microorganisms, and the absence of a comprehensive strategic management plan make PDS an appealing area of investigation. PDS can be isolated, characterized, and tested for phytochemicals using analytical methods that have been developed to treat a variety of illnesses. This approach considers the quantitative traits of plant components that substantiate their positive effects on health. PDS, which includes tannins, alkaloids, and polyphenols, are excellent at fighting bacterial infections, which makes them attractive candidates for use as antibiotic resistance regulators or antimicrobials.[58]

In the fight against antimicrobial resistance, new technologies are continuously replacing conventional antimicrobials. Nanotechnology-driven innovations offer hope for overcoming drug resistance in both medical and veterinary domains. Metallic particle-based nanostructures have been developed to combat microbial infections. The effectiveness of these nanostructures is dependent on the interaction between the nanoparticles (NPs) and bacteria. A comprehensive understanding of the physicochemical characteristics of NPs and the biological aspects of microorganisms is essential for creating efficient nanomaterials. However, it is imperative to address the potential risks associated with using NPs in healthcare settings.[59]

Antibiotic resistance is currently a major global health and economic burden, as are the illnesses it causes. Therefore, the hunt for new therapeutic agents to combat resistant infections has become necessary as a result of the abuse of antibiotics, which has raised resistance. The therapeutic use of antimicrobial peptides (AMPs) against infections with treatment resistance appears promising. Antimicrobial peptides (AMPs) are low molecular weight oligopeptides that exhibit broad-spectrum antimicrobial activity against pathogenic microbes. As nonspecific antibodies, AMPs specifically target bacterial components that facilitate immune response, thus acting as the first line of defense against invasive pathogenic microorganisms. Due to their diverse nature and potent antimicrobial properties, AMPs represent promising candidates for alternative therapeutic approaches. They can be utilized independently or in combination with various biomaterials to enhance therapeutic efficacy. Furthermore, AMPs hold potential applications in vaccine development.[60]

In the forthcoming decades, clinical microbiology will rely on two fundamental pillars, namely, the detection and monitoring of antimicrobial resistance. The advent of specific technologies such as whole genome sequencing (WGS) and mass spectrometry, along with the establishment of comprehensive national and international databases encompassing data on antimicrobial resistance from across the globe, has enabled the utilization of bioinformatics for investigating antimicrobial resistance in microorganisms associated with human pathology.[61,63,64]

CONCLUSION

Antibiotic resistance, in particular, continues to grow and spread throughout all borders. This is a problem that has several parameters; it is not a single problem. In order to combat AMR at the local, national, and worldwide levels, coordinated efforts and diverse collaborations are needed. Antibiotics must not be promoted unethically, and methods must be put in place to prevent their excessive or inappropriate use. Inactivation, silencing, and editing of resistance genes are only a few of the innovative targets and techniques that have been tested to increase antibiotic efficacy. Importantly, the majority of the cutting-edge alternatives do not promote antibiotic resistance. Regulatory agencies,

institutions, and governments are working to explore a variety of new strategies to counteract prevailing and emerging resistance, but it will be some time before we can assess their effectiveness, both individually and in combination.

Enhanced approaches for sampling and analyzing microbial populations and metagenomic libraries are imperative to gain deeper insights into the drivers of resistance gene dissemination and elucidate the interrelationships among resistance determinants across these populations. The development of improved algorithms and the utilization of bioinformatics techniques hold great promise in establishing connections between various environmental niches and determining factors contributing to antibiotic resistance. These bioinformatics tools offer the potential to rapidly extract valuable information regarding resistance genes and their associated products from a vast array of bacterial species isolated from diverse sources such as hospitals and the environment. Furthermore, these tools enable the identification of mobile genetic elements linked to resistance, facilitating a more comprehensive understanding of the molecular basis of drug resistance.

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