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ANALYSIS OF PRINCIPLES FOR IMPROVING MEASURES TO COMBAT ANTIBIOTIC-RESISTANT MICROBES

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Abstract. Antimicrobial resistance is becoming more prevalent worldwide and is linked to higher rates of morbidity and mortality in both hospital and community settings. The emergence of superbugs and the spread of antibiotic resistance to various environmental niches have made effective control methods even more challenging. Antimicrobial resistance control and prevention strategies at the international, national, and local levels have been recommended. The main suggested strategies include bettering hand hygiene, regulating the availability of antibiotics over-the-counter, using antimicrobials sensibly, and enhancing infection prevention and control. Innovation in novel medications and vaccinations is required, as is a thorough understanding of the mechanisms underlying resistance. Fighting antimicrobial resistance requires a comprehensive, cooperative regulatory strategy. Since they have prevented millions of deaths from infectious diseases, antibiotics are among the most significant discoveries of the 20th century. Due to strong selection pressure brought on by the growing use and abuse of antibiotics throughout time, microbes have evolved acquired antimicrobial resistance (AMR) to numerous medications. AMR is mostly acquired and transmitted through human-to-human contact both inside and outside of healthcare facilities. Through a variety of drug-resistance mechanisms, a vast array of interrelated healthcare and agricultural factors control the development of AMR. One of the main causes of AMR's introduction and spread has been the uncontrolled use of antibiotics in animal feed. Antimicrobial-resistant bacteria are becoming more commonplace globally and pose a latent pandemic threat to public health, requiring. In order to prevent a postantibiotic period from becoming more than just a 21st-century apocalyptic nightmare, coordinated cooperation inside and between numerous national and international institutions is desperately needed. The processes and contributing aspects of microbial resistance, as well as important tactics to counteract antimicrobial resistance, are highlighted in this narrative review.

Keywords. Antibiotics, antimicrobial resistance, resistance mechanisms, resistance causes, and resistance-fighting strategies.

Introduction. The most amazing medical advancement of the 20th century, antibiotics are the "magic bullets" for combating bacteria. Millions of lives have been saved from bacterial illnesses since the discovery of antibiotics, which altered the therapeutic paradigm. Antibiotics have undoubtedly been a blessing to humanity; in addition to their medical applications, they have long been used for a variety of purposes, such as animal husbandry and production as preventative measures in many developing and impoverished nations. Microorganisms have evolved antimicrobial resistance (AMR) as a result of its increased use and misuse. The ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to flourish and keep growing in the face of medications intended to eradicate them is known as the phenomenon of antimicrobial resistance. In addition to being challenging to cure, infections brought on by organisms resistant to antibiotics always have a higher risk of serious disease or even death. Antimicrobial agents come in a variety of forms, such as antibiotics, antifungals, antivirals, disinfectants, and food preservatives, which either kill or inhibit the growth and multiplication of microorganisms. More often than any other class of antimicrobials, antibiotics are used to treat bacterial infections and antibiotic resistance [1-6]. The emergence of germ resistance is a constant challenge to the development of antibiotics. The most successful treatments have already been jeopardized by the emergence of MRSA and resistant Pseudomonas aeruginosa. According to recent findings, AMR is expanding and exhibiting a shifting susceptibility pattern.New Delhi metallo-β-lactamase 1 (NDM-1) positive superbug development Enterobacteriaceae have made treating these infections even more challenging. The incidence of antimicrobial-resistant bacteria has reached an unprecedented level globally, posing a silent pandemic threat to public health and requiring immediate action. There are few treatment options for illnesses brought on by bacteria resistant to antibiotics, which has a substantial financial burden and causes considerable morbidity and mortality. The lack of new, innovative antimicrobials to treat life-threatening infections caused by resistant microorganisms contrasts sharply with the demand. Surveillance and monitoring, reducing the use of over-the-counter antibiotics and antibiotics in food animals, providing access to high-quality, reasonably priced medications, vaccinations, and diagnostics, and enforcing laws are all immediate measures to prevent antimicrobial resistance [7-13]. Based on their own logic, pharmaceutical companies have given up on finding new antibiotics and have stopped adding to their substantial antibiotic inventory since the 1980s. Fluoroquinolone was introduced to the market in 1987 and was one of the final broad-spectrum antibiotics discovered in the 1980s. There hasn't been much progress since then, and there aren't many new antibiotic families in the works. Antibiotic use is linked to the emergence of resistance, suggesting that minimizing needless antibiotic use can significantly lower resistance. Since there hasn't been any notable discovery of new compounds in recent decades, it is now critical to maintain the effectiveness of currently available antimicrobials because they are essential tools for treating and preventing infectious diseases. The foundation, methods, and contributing elements of microbial resistance as well as important tactics to counteract antimicrobial resistance are highlighted in this narrative review [14-22].

The main purpose of the presented manuscript is to provide a brief analysis of the principles of improving measures to combat antibiotic-resistant microbes in medical practice based on the results of authoritative scientific works.

Antibiotic Resistance and Major Antibiotic Discovery Timeline. In 1910, Paul Ehrlich discovered salvarsan and neosalvarsan, a synthetic prodrug, to treat syphilis caused by

Treponema pallidum. This discovery heralded the beginning of the modern era of antibiotics. Later, salvarsan was gradually supplanted by prontosil, a sulfonamide prodrug that was developed by bacteriologist Gerhard Domagk. The first comprehensive assessment of soil microorganisms and their capacity to produce chemicals with antibiotic activity is attributed to American microbiologist and biochemist Selman Waksman in the 1930s. He described an antibiotic as "a compound made by a microbe to destroy other microbes" and discovered several antibiotics from filamentous actinomycetes that live in the soil, including streptomycin, a commonly used antibiotic against tuberculosis. The golden age of antibiotic research, which lasted until the mid-1950s, began in 1928 when Scottish physician and microbiologist Sir Alexander Fleming discovered penicillin from a mold known as Penicillium rubens [2-11]. The majority of the antibiotics still in use today were found during what is known as the "Golden Age" of antibiotic discovery, which ran from the 1940s to the 1960s. Since then, the development of drug-resistant organisms has coincided with a slow decrease in the discovery of new antibiotics. Antibiotic-resistant bacteria have been identified practically since the beginning of the antibiotic era. Introduced in 1980, carbapenem is a type of β-lactam that has been kept as a backup medication to treat infections caused by enterobacterales, particularly those that are resistant to cephalosporins. Since 2006, reports of carbapenem-resistant enterobacterales (CRE) from various nations have been made due to its increased use during the 1990s and 2000s. The pharmaceutical industry only generated new classes of antibiotics for two decades, from 1960 to 1980, according to the timeline of antibiotic discovery. After that, the rate of discovery drastically decreased until recently. Critics have enough justification to foresee an impending postantibiotic age due to the disproportionate ratio of drug-resistant organisms to the amount of accessible antibiotics [14-22].

Antibiotic Resistance's Basis. Bacteria acquire antibiotic resistance as an evolutionary reaction to the threat posed by therapeutic antibiotics. From a therapeutic standpoint, all targeted pathogens are initially sensitive to an antibiotic, but germs become resistant to it with prolonged treatment. From an evolutionary standpoint, bacteria either (1) acquire foreign DNA by horizontal gene transfer (HGT) that codes for resistance determinants, or (2) modify chromosomal genes to adapt to the effects of antibiotics. Antibiotic resistance is primarily caused by mutations in three types of genes: genes that encode the antibiotic's targets, transporters of the antibiotic, and regulators that suppress the expression of transporters (such as multidrug efflux pumps and antibiotic-modifying enzymes). The idea that commensal or ambient bacteria are the source of the antibiotic-resistance gene or genes that are transferred to human pathogenic bacteria by horizontal gene transfer (HGT) is intriguingly supported. Numerous antibiotics are known to be spontaneously produced by bacteria found in the environment. They must also have antibiotic-resistant genes in order to protect themselves from the effects of self-synthesised antibiotics; otherwise, their own antibiotics would have killed them [11-21].

Bacterial Antibiotic Resistance Mechanisms. Enzymatic modification or inactivation of the antibiotic, decreased binding affinity of the antibiotic to its bacterial molecular targets, horizontal gene transfer via plasmids carrying multidrug resistance (MDR)-associated genes between species, alterations in the permeability of the bacterial cell surface, overexpression of efflux pumps capable of identifying and expelling a wide range of antibiotics with diverse mechanisms of action, and genetic variations such as polymorphisms or insertions in DNA sequences encoding transcriptional regulators are some of the antibiotics. Bacterial pathogenicity, metabolism, and multidrug resistance are all significantly influenced by efflux pumps, which are essential membrane transporters. These pumps stop exogenous chemicals like antibiotics, disinfectants, and detergents from reaching their intended biological targets by actively lowering

their intracellular concentrations. Consequently, efflux transporters have emerged as interesting targets for the creation of novel inhibitors to fight infectious disorders linked to MDR [1-14].

Possible Adverse Reactions to Antimicrobial Agents Based on Venom. Although chemicals generated from venom have the potential to tackle antibiotic resistance, it is important to take into account any potential negative effects on humans. Numerous venom peptides are cytotoxic to mammalian cells, which can result in immunogenic reactions, hemolysis, or neurotoxicity. For example, bee venom has demonstrated promise antibacterial benefits, but at high dosages, it may produce cytotoxicity and allergic responses. Similar to this, lionfish venom has antimicrobial bioactive peptides, but its harmful side effects—such as hemolysis and pain—remain a worry. Peptides from spider venom also show antibacterial and anti-inflammatory properties, although their safety profiles need more research. Therefore, even if venoms have the potential to fight antibiotic resistance, their negative effects need to be carefully considered before being used in clinical settings [4-10]. Researchers are using peptide changes to improve selectivity for bacterial membranes while reducing damage to human cells in order to reduce toxicity risks. It has been demonstrated that chemical changes, such as structural optimization and amino acid substitutions, increase antibacterial effectiveness while lowering cytotoxicity. Furthermore, self-assembled peptide nanostructures and other nanocarrier-based delivery systems have been created to regulate drug release and reduce off-target effects. Together, these strategies resolve safety issues and increase the antimicrobial peptides' clinical viability. Furthermore, the successful development of medications derived from venom, such as Captopril and Ziconotide, shows that venoms can be safely used for therapeutic purposes with careful clinical testing. Before venom-based antibiotics are used therapeutically, more research is necessary to assess their clinical safety profile [17-21].

Strategies to Combat Antibiotic Resistance. Antibiotic resistance remains a critical challenge in global healthcare, threatening the effectiveness of treatments and increasing the burden of resistant infections. While no single approach can completely eliminate this problem, various strategies can help mitigate its spread and impact. Antibiotic overuse is a major driver of resistance evolution, as epidemiological studies have shown a direct link between consumption and the emergence of resistant strains. Resistance genes can transfer between bacterial species via horizontal gene transfer or arise naturally through mutations, which are processes exacerbated by inappropriate prescribing practices and suboptimal dosing. These factors not only enhance pathogen virulence, but also accelerate the dissemination of resistance determinants [8-13]. Improving antibiotic stewardship, strengthening infection prevention strategies, and developing alternative therapeutics like phage therapy and immunotherapies are all necessary to address these issues. Campaigns to raise public awareness and educate people about the responsible use of antibiotics are also essential in reducing resistance. The study of new antimicrobial strategies has become necessary due to the diminishing effectiveness of traditional antibiotics. This section looks at new approaches to fight antibiotic resistance, such as bacteriophage therapy, CRISPR-Cas systems and their connection to resistance mechanisms, microbial-based therapies, stem cell applications, immunotherapeutic modalities, photodynamic antimicrobial techniques, quorum quenching mechanisms that interfere with bacterial communication networks, and bioactive compounds derived from animal venoms [14-24].

Discussion. The fast rise of multidrug-resistant (MDR) bacterial infections is driving the growing global health dilemma of antibiotic resistance, which calls for quick and creative solutions. This article thoroughly investigates the various strategies used by bacteria to avoid the effects of antibiotics, such as changes in the permeability of cell membranes, overexpression of efflux pumps, biofilm development, target site modifications, and enzymatic antibiotic degradation. Membrane transport systems, including ATP-binding cassette (ABC) transporters,

resistance–nodulation–division (RND) efflux pumps, major facilitator superfamily (MFS) transporters, multidrug and toxic compound extrusion (MATE) systems, small multidrug resistance (SMR) families, and proteobacterial antimicrobial compound efflux (PACE) families, are specifically highlighted. Quorum quenching (QQ), probiotics, postbiotics, synbiotics, antimicrobial peptides (AMPs), stem cell applications, immunotherapy, antibacterial photodynamic therapy (aPDT), bacteriophage, and other novel therapeutic approaches are also examined in the review, along with the worldwide burden of MDR pathogens [3-11]. This review also addresses new antimicrobial agents as potential substitutes for traditional antibiotics, including substances produced from animal venom and nanobiotics. Analysis of the interaction between CRISPR-associated proteins (Cas) and clustered regularly interspaced short palindromic repeats (CRISPR) in bacterial adaptive immunity reveals potential targets for focused genetic treatments. This study highlights the need for multidisciplinary cooperation between biomedical scientists, researchers, and the pharmaceutical sector to propel the development of novel antibacterial medicines by summarizing recent developments and new approaches. In the end, this thorough analysis offers a road map for further study, highlighting the critical need for sustainable and collaborative strategies to fight antibiotic resistance and protect world health. Even with these encouraging options, there are still a lot of obstacles to overcome [13-19]. Major obstacles include the high costs of creating and marketing new treatments, the requirement for stringent regulatory approvals, and the possibility of resistance evolving against innovative treatments. Furthermore, further research is required to comprehend the long-term effectiveness and ecological impact of these interventions due to the complexity of microbial ecosystems. Future initiatives should concentrate on improving the price and scalability of new antibiotics, maximizing combination treatments to stop resistance, and encouraging international cooperation to carry out long-term antibiotic stewardship initiatives [20-25].

Conclusions. The misuse of antibiotics and the halt in the discovery of new drugs are the main causes of the antibiotic resistance dilemma, which continues to be a major worldwide health concern. In addition to highlighting alternative tactics like quorum-sensing inhibitors, probiotics, antimicrobial peptides, venoms, nanobiotics, bacteriophages, CRISPR-Cas systems, immunotherapy, and photodynamic therapy, this review explored the intricate resistance mechanisms of multidrug-resistant pathogens. It was also emphasized how important the environment is both a source of new antimicrobials and a reservoir for resistance genes.

Antimicrobial resistance is a complicated issue with a wide range of underlying causes. It is a significant contributor to health issues that either directly or indirectly increase costs to the individual and the community. The greatest way to stop the spread of infections and, consequently, AMR is still prevention. It is necessary to develop new, effective chemicals and new diagnostic technologies in addition to using current antimicrobial medications sensibly. To combat the worldwide spread of antibiotic resistance, patients, prescribers, and individuals must work together with international regulators and policy makers.

A coordinated, multidisciplinary effort is required to address this situation. To create novel solutions, raise awareness, and put sustainable policies into action, cooperation between healthcare professionals, researchers, legislators, and the general public is crucial. We can secure the development of new therapies, preserve the effectiveness of current antibiotics, and defend public health for present and future generations by developing these strategies.

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