Research & Reviews: Drug Delivery

# Recent Advances in Bacterial Drug Resistance and Antibiotics

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Review Article

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## ABSTRACT

The crisis of antibiotic resistance affects health worldwide and necessitates the development of innovative medicines. Since their discovery and widespread use in the early to mid-20th century, antibiotics have been a crucial weapon in the struggle against infectious diseases. Similarly, the proliferation of antibiotic usage has led to a significant apprehension regarding drug resistance and its implications for human well-being. The majority of the pharmacological leads under investigation today are alterations of recognized antibiotics, many of which come from organic sources. Several antibacterial agents and drug delivery technologies have demonstrated encouraging outcomes. Nano-drug delivery methods for antibiotics offer several advantages compared to traditional antibiotics. These methods have the potential to reduce antibiotic resistance and prolong the effectiveness of novel antibiotics. Additionally, they enable precise and targeted drug administration. This review elucidates the molecular mechanisms underlying the utilization of multiple approaches in the fight against drug-resistant bacteria. Additionally, it discusses the latest advancements in antimicrobial materials and drug delivery systems for diverse carriers.

**Keywords:** Antibiotics; Anti-bacterial; Anti-microbial resistance; Drug resistant bacteria; Clinical advancements; Polymers; Nanoparticles

## INTRODUCTION

An infection caused by bacteria is a common medical condition that can manifest in a variety of ways. Humans have utilized natural remedies for centuries to treat microbial diseases and superficial infections with preparations made from molds, plants, and dirt [1]. In medicine, infections caused by bacteria are treated with antibiotics, which over time have become progressively resistant to all treatments. Polymyxin, vancomycin, and other antibacterial agents considered to be the "last line of defense" have simultaneously contributed to the development of Multi-Drug Resistant (MDR) microorganisms. To effectively develop these adjuvants, it is imperative to possess a comprehensive understanding of the chemical properties of the adjuvant molecule as well as the biological mechanisms underlying resistance. This research focuses on the mechanisms involved in the implementation of diverse strategies aimed at combating drug-resistant bacteria. Furthermore, this paper presents a comprehensive overview of recent advancements in antimicrobial materials and drug delivery techniques across various carriers. Furthermore, this study explores the fundamental elements involved in addressing antimicrobial resistance, while also analyzing the existing obstacles and future prospects within this field.

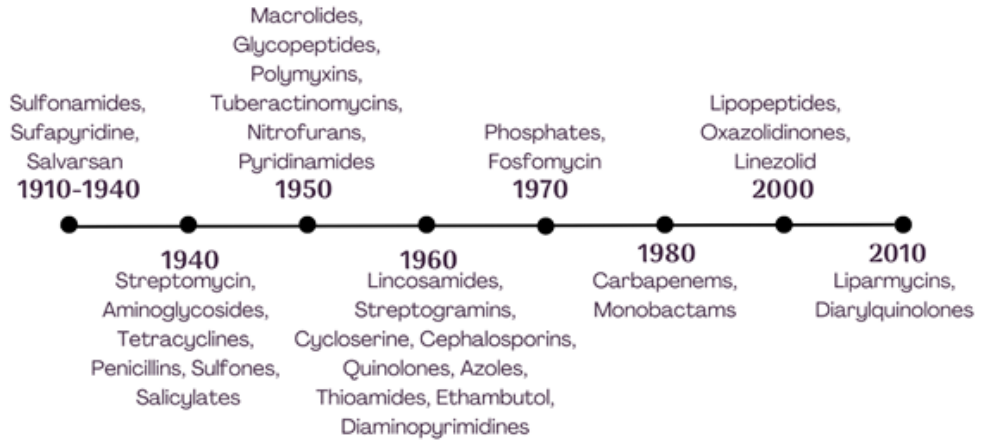
## LITERATURE REVIEW

### An overview of the development and discovery of antibiotics

Microorganisms exhibit an extensive range of diversity that appears to be limitless. Renowned microbiologists, including Louis Pasteur (1822-1895) and Robert Koch (1843-1910), held the belief that in order to prosper amidst competition, microorganisms must develop potent mechanisms, referred to as "antibiosis," to counteract their adversaries. It was postulated that microorganisms capable of withstanding the competitive environment had acquired a form of resistance against the weaponry employed by their adversaries. The term "antibiotic," derived from the Greek words' "anti" meaning against and "bios" meaning life, was introduced in 1942 by Selman Waksman (1888-1973), a renowned scientist. According to his statement, this substance is produced by bacteria in small quantities with the purpose of either killing or impeding the growth of other species. Based on the aforementioned criteria, the phrase was employed over the course of the subsequent two decades. Despite the continued usage of the term, its definition has broadened to include the various semi and fully-synthetic "antibiotics" manufactured by the pharmaceutical sector.

In initial decades, *i.e.,* from 1890 to 1910, Emmerich and Low utilized "pyocyanase," an extract from *Pseudomonas aeruginosa*, to treat infectious disorders in the first contemporary clinical method [2]. During the 1940's, medical practitioners were introduced to the initial antibiotic, penicillin, which was derived from the fungal species known as *Penicillium*. The clinical utilization of antibiotic chemotherapy became widely embraced subsequent to the identification of streptomycin and tetracycline, derived from *Actinomycetes*, during the 1940's and 1950's, respectively. The efficacy of these drugs extended beyond the bacillus responsible for tuberculosis, as they demonstrated effectiveness against a range of pathogenic microorganisms (Figure 1).

**Figure 1.** Discovery of antibiotics over a century.

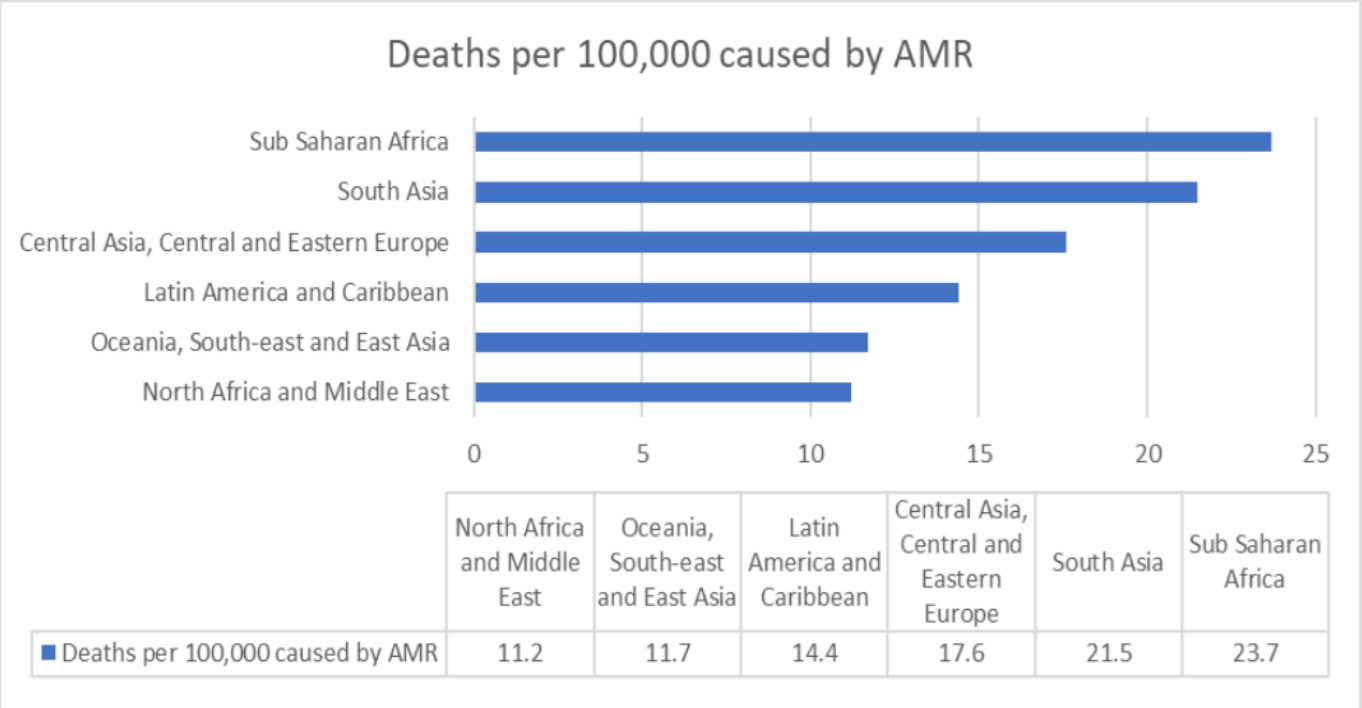


Currently, the European Medicines Agency (EMA) Food and Drug Administration (FDA) and the Food and Drug Administration (FDA) have granted approval for the systemic use of 22 antibiotic classes, with the exception of mycobacterial infections. There are four classes within this categorization that are of synthetic origin, while seventeen classes are derived from natural sources. Additionally, one class, namely nitroheterocycles, is unique as it encompasses both synthetic and natural components [3].

## The emergence of antimicrobials resistance

Antimicrobials encompass a diverse range of pharmaceutical agents, which include antibiotics, antivirals, antifungals, and substances with antiparasitic properties. Antimicrobials serve a dual purpose in the realm of disease management, encompassing both preventive measures and therapeutic interventions. Within the field of microbiology, the term "Antimicrobial Resistance" (AMR) pertains to the capacity of bacteria and other microorganisms to endure the potentially fatal consequences of an antimicrobial medication that they were previously susceptible to. In contrast, the issue of Antimicrobial Resistance (AMR), which has experienced a notable rise in prevalence in recent times, seems to be posing a significant threat to the continued effectiveness of this historically significant medication. Antimicrobial Resistance (AMR) is not a concept that can be characterized as novel or revolutionary. The discovery of antibiotics occurred several years subsequent to this development. The initial identification of penicillin resistance occurred in staphylococci, streptococci, and gonococci. The emergence of penicillin-resistant *S. aureus* took place in 1942, shortly after the commercial availability of penicillin in 1941 [4]. However, the extent of its destruction was not fully understood until a few decades ago, when hospitals began experiencing outbreaks of infections caused by superbugs resistant to a broad range of antimicrobial drugs. The term "superbugs" is frequently employed when referring to bacteria that are the underlying cause of AMR. Antimicrobial resistance has rapidly become one of the most urgent issues affecting the current condition of global health. According to the World Health Organization (WHO), antimicrobial resistance is presently a global health concern that, if not addressed, could result in millions of deaths per year by 2050 (Figure 2).

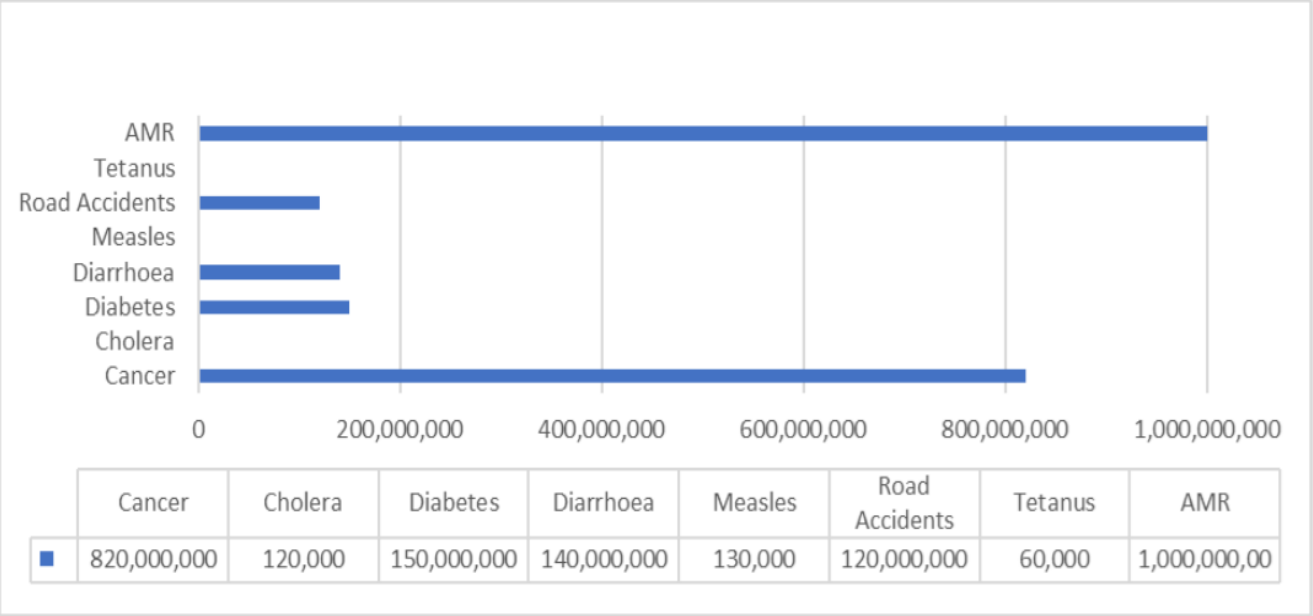
**Figure 2.** Number of deaths reported due to AMR as per the data obtained from "Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis".




| | North Africa and Middle East | Oceania, South-east and East Asia | Latin America and Caribbean | Central Asia, Central and Eastern Europe | South Asia | Sub Saharan Africa |
|---|---|---|---|---|---|---|
| Deaths per 100,000 caused by AMR | 11.2 | 11.7 | 14.4 | 17.6 | 21.5 | 23.7 |

In order to better understand and address this healthcare catastrophe, it is necessary to conduct a comprehensive re-evaluation of the existing AMR situation. We are rapidly approaching an antibiotics crisis as reports of increased resistance to routinely used antibiotics have emerged worldwide, especially for infections like UTIs, STIs, sepsis, and some forms of GI infections (Figure 3).

**Figure 3.** Comparison of number of deaths by different diseases with respect to AMR as per the data obtained from "Antimicrobial resistance: Tackling a crisis for the health and wealth of nations, 2019".




| | Cancer | Cholera | Diabetes | Diarrhoea | Measles | Road Accidents | Tetanus | AMR |
|---|---|---|---|---|---|---|---|---|
| ■ | 820,000,000 | 120,000 | 150,000,000 | 140,000,000 | 130,000 | 120,000,000 | 60,000 | 1,000,000,00 |

Antimicrobial resistance is a complex issue requiring a comprehensive solution. Even if the creation of novel antimicrobial agents is crucial, it is insufficient on its own. Antimicrobial stewardship programs and infection control measures are crucial methods for preventing the spread of drug-resistant diseases. It is imperative that studies on Antimicrobial Resistance (AMR) mitigation involve the active participation of researchers from diverse disciplines such as chemistry, microbiology, pharmacology, biomaterial science, immunology, and others. In order to advance the development of novel vaccines, alternative therapeutic interventions, and antibiotics, it is imperative for researchers to engage in collaborative efforts. The significance of the contributions made by various societal groups, including physicians, chemists, healthcare professionals, policymakers, policy experts, analysts, and end-users (patients), is comparable to that of researchers. The most effective approach to addressing the persistent issue is by adopting a multidisciplinary and collaborative methodology.

## Why AMR is a global challenge?

Antibiotic resistance remains a severe risk to the health worldwide because it fosters the emergence and spread of germs that are resistant to current treatments. Superbug infections have increased due to the COVID-19 pandemic, undoing all gains obtained in the fight against lethal viruses. New antibiotics are necessary, but we also need to alter how we use them in order to keep them from eventually losing their efficacy.

Antibiotic resistance has significant adverse impacts on national economies and health systems, including higher medical expenses, prolonged hospital stays, and a higher death rate. In the year 2019, the global mortality rate attributed to antimicrobial resistance amounted to 4.95 million fatalities, with 1.27 million of these deaths directly linked to the presence of microorganisms that exhibited resistance against commonly employed antibiotics. One in five of those who died were children under the age of five. Antibiotic resistance was ranked as one of the top dangers to world health, food security, and development by the World Health Organization (WHO) in 2018 [5].

Patient outcomes are significantly impacted by antimicrobial resistance, including higher rates of morbidity and mortality. Resistant bacteria increase the likelihood of patients experiencing serious health problems and raise the risk of death compared to non-resistant bacteria. In situations where the illness is more resistant and the patient is more susceptible, these unfavorable results are considerably more severe. Antimicrobial resistance mortality rates are predicted to surpass those of the main global causes of death by 2050 [6].

## Genesis of antimicrobial resistance

Antibiotic resistance can be genetic or phenotypic. Phenotypic resistance occurs when bacterial cells adapt to environmental stress, such as antibiotics. Removing stress reverses adaptive resistance. Phenotypic resistance includes generic variables like biofilm formation, which slows bacteria's growth rate and makes them more resistant to antibiotics and biocides, and specific factors like *E. coli*'s increased aminoglycoside resistance in anaerobic conditions. Another prominent example of phenotypic resistance is the induced manufacture of B-lactamases in response to B-lactam antibiotics, which is a defensive mechanism that bacteria may switch on and off to preserve energy.

## Mutation-based resistance

Bacterial mutations depend on the population's density and reproducing rate. Mutations cause antibiotic resistance, especially in chronic illnesses. Some drugs and bacterial species are more prone to mutation-induced resistance. Antibiotic concentration and environment affect mutation rate. Mutation-induced enterococci resistance to vancomycin and aminoglycosides is recent. However, chronic infections usually require many antibiotics. The risk of a cell developing resistant to both medicines concurrently is the product of their mutation rates, not the sum.

## Resistance emerging as a result of new genetic evidence

There are three ways for bacteria to acquire new genes:

**Transformation:** It happens when a bacterial cell gathers up DNA released by a dead cell and incorporates it into its own chromosome. This process occurs only in a few bacterial species, including *Streptococcus*, *Neisseria*, *Helicobacter*, and *Acinetobacter*, and only under certain environmental or nutritional conditions. Competent bacteria are those that can conduct this function naturally. While this mechanism is less prevalent than others, it can be quite effective in some bacterial-antibiotic combinations, such as the development of resistance to benzyl penicillin or amoxicillin (and ampicillin) in *Streptococcus pneumoniae* and gonococci.

**Transduction:** After infecting a bacterial cell, a bacteriophage may enter a latent condition within the host and integrate its nucleic acid into the host's genetic material. This state can be terminated if the cell is subjected to a certain trigger, which causes the phage to proliferate and destroy the host cell. The resultant phage particles can then infect new hosts, potentially transmitting genetic material from the original host, including antibiotic resistance genes. This process, known as transduction, is species-specific and cannot transmit resistance between bacteria. Transduction is well known for transferring B-lactamase genes across *Staphylococcus aureus* strains, but it can also transfer genes responsible for the production of toxins and other virulence factors.

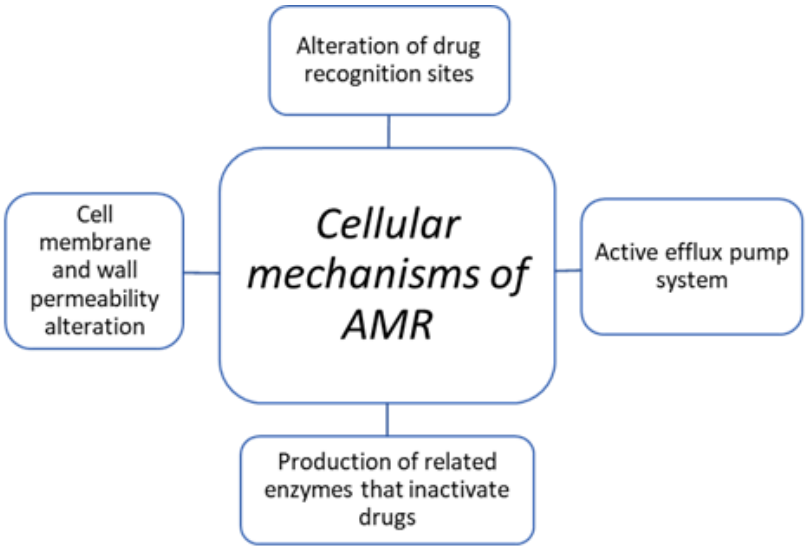
**Conjugation:** Plasmids are non-essential DNA molecules found in bacteria that carry antibiotic resistance, toxin synthesis, and fimbriae creation genes. Conjugation, a horizontal gene transfer method, allows for the transfer of plasmids from one bacterium to another. During conjugation, the donor bacterium attaches to the receiving bacteria *via* a sex pilus, and a copy of the plasmid is given to the recipient. This procedure can occur between different strains of the same species or even between distinct bacterium genera, making it an effective route of gene transfer.

## The cellular mechanisms underlying antibiotic resistance

Bacterial resistance commonly emerges as a result of antimicrobial therapy, enabling bacteria to evade eradication by antibiotics. It is crucial to acknowledge that the emergence of bacterial tolerance and resistance is occurring rapidly on a global scale due to the persistent misuse and excessive utilization of conventional antimicrobial therapies [7]. Based on the

conclusions drawn from a report, it has been observed that the emergence of antibiotic-resistant bacteria can transpire within a span of five years subsequent to the introduction and accessibility of a novel antibiotic in the market. As per the assessment conducted by the World Health Organisation (WHO), antimicrobial resistance emerged as a prominent health concern among the top 10 global risks in 2019 [8]. Figure 4 illustrates the four discrete mechanisms of drug resistance at the protein level.

**Figure 4.** Cellular drug resistance mechanism.




The increasing consumption of antibiotics in every region of the globe exacerbates the worldwide problem of the ineffectiveness of conventional antimicrobial treatments. Multiple resistance mechanisms have currently been established by MDR bacteria to fend against the majority of antibiotics on the market. Different explanations, such as genetic, metabolic, and biochemical factors, might be used to explain these resistance mechanisms. Genetic mechanisms describe the numerous ways in which bacteria might acquire resistance, including mutations in their own genetic code, chromosome transmission vertically, plasmid or transposon horizontal transmission, and integron acquisition of external resistance genes [9].

The physiological level plays a crucial role in determining the "Viable But Non-Culturable state" (VBNC) of bacteria, with the metabolic mechanism being the primary determinant. The state referred to as the "VBNC" is a specific survival strategy employed by bacteria when faced with adverse conditions. The efficacy of the majority of antibacterial medications in this particular state is limited to metabolically active bacteria. Consequently, the targeted bacteria have the ability to evade the effects of antibiotics and transition into a dormant phase. When bacteria are subjected to such conditions, their growth and metabolism exhibit a significant reduction in activity or may even come to a complete halt [10]. The primary factor influencing the resistance of microorganisms to antibiotics is the biochemical processes that take place at the protein level. These mechanisms facilitate the ability of bacteria to generate and secrete operational proteins or to alter their own structural proteins.

## DISCUSSION

### Antimicrobial compounds and materials

According to available data, the overwhelming majority of antibiotics that have been authorised in recent years were discovered prior to 2010. Due to its undeniable significance, Antimicrobial Resistance (AMR) has prompted a worldwide drive for the rapid development of novel drugs and treatments. However, it is important to note that the issue of antibiotic resistance is a persistent challenge that cannot be definitively resolved. Consequently, the pursuit of innovative antimicrobial treatments or strategies to combat bacterial infections will remain an ongoing endeavour indefinitely. This article examines the process of choosing and executing alternative antibiotic treatment approaches in response to bacterial resistance. In recent years, there has been a significant surge in research pertaining to alternative approaches for combating bacterial resistance, specifically in the realm of non-traditional antibiotic treatment strategies.

**Drugs that inhibit enzyme:** The mitigation of the drug resistance problem can be achieved through the discovery and development of efficacious enzyme inhibitors targeting bacteria that exhibit resistance by producing enzymes that diminish the effectiveness of antibiotics. Despite possessing a -lactam ring structure, clavulanic acid, which is the initial broad-spectrum -lactamase inhibitor employed in clinical settings, exhibits limited antibiotic efficacy. The co-administration of clavulanic acid with other antibiotics resulted in a heightened efficacy of the latter [11]. Clavulanic acid was two to twenty-five times more potent than other -lactamase inhibitors at penetrating the cell walls of various bacteria. Combining -lactam antibiotics with clavulanic acid was effective in treating -lactam-resistant bacteria. First used in the clinic in 1981, amoxicillin-clavulanic acid is still the sole oral formulation available in the group of -lactam and -lactamase inhibitors [12].

The research conducted by Sun and colleagues revealed that the anti-inflammatory medication known as auranofin effectively hindered the activity of NDM-1 by displacing zinc ions within the protein's active site. The addition of auranofin resulted in a significant reduction in the Minimum Inhibitory Concentration (MIC) of meropenem in NDM-1 producing *Escherichia coli*. This effect was quantified using a Fractional Inhibitory Concentration Index (FICI) of 0.156. Bacterial strains harbouring the Mobilised Colistin Resistance-1 (MCR-1) gene exhibited a Fractional Inhibitory Concentration Index (FICI) of approximately 0.125 upon exposure to a combination of auranofin and polymyxin. This synergistic interaction significantly reduced the Minimum Inhibitory Concentration (MIC) of polymyxin. This study proposes that the combination of auranofin and carbapenems may serve as a potential strategy to reinstate the effectiveness of antibiotics against multidrug-resistant bacteria. In their study, El-Halfawy, et al. successfully identified the bioactive compound MAC-545496 through the implementation of a range of high-throughput screening platforms. This approach was employed to address the challenge of Methicillin-Resistant *Staphylococcus aureus* (MRSA) strains that exhibit resistance towards -lactam antibiotics. The Minimum Inhibitory Concentration (MIC) of cefuroxime against *Staphylococcus aureus* was observed to decrease significantly from 512 g/mL to 8 g/mL when combined with a concentration of 0.03 g/mL of MAC-545496. Furthermore, it was demonstrated that a concentration of 0.06 g/mL of MAC-545496 effectively restored susceptibility to β-lactam antibiotics in Methicillin-Resistant *Staphylococcus aureus* (MRSA) strains. Furthermore, it has been demonstrated that the compound MAC-545496 exhibits efficacy against over ten strains of clinical isolates of *S. aureus* when administered in combination with cefuroxime and oxacillin.

Hydrogen Sulphide ($H_2S$), an exceedingly reactive gaseous compound, exhibits the capacity to shield bacteria from oxidative stress. Moreover, enzymes responsible for the generation of $H_2S$ can effectively counteract the antibacterial properties of pharmaceutical agents. In their study, Giorgia Croppi, et al. employed a high-throughput drug screening method to investigate the inhibitory effects of various compounds on *E. coli* 3-Mercaptopyruvate Transsulfurase (eMST). Through this approach, the researchers successfully identified pioglitazone, an FDA-approved medication commonly prescribed for the management of type II diabetes, as the initial active inhibitor of eMST among a vast pool of over 26,000 compounds. The inhibitor was examined at the cellular and bacterial levels, revealing its ability to augment the bactericidal efficacy of antibiotics. In their study, Shatalin, et al. conducted a screening of enzymes responsible for bacterial hydrogen sulphide production in order to identify potential inhibitors [13]. Through their investigation, they uncovered a specific group of inhibitors known as bCSE inhibitors, which exhibited their inhibitory effects through a metamorphic mechanism. The discovery that bCSE is essential for the production of Hydrogen Sulphide ($H_2S$) in both *S. aureus* and *P. aeruginosa* has prompted the development of bCSE inhibitors. These inhibitors have been found to augment the efficacy of various antibacterial medications. The findings of their study demonstrated that bacteria exhibiting resistance released a notably higher quantity of Hydrogen Sulphide ($H_2S$) compared to their non-resistant counterparts. The study revealed that the concurrent administration of multiple antibiotics exhibited the capacity to diminish the rates of treatment failure in cases of acute infections, as it impeded the bacteria's viability in the presence of these medications.

**Polymers with cationic chains:** Cationic polymers possessing intrinsic antibacterial properties encompass Polyquaternary Ammonium Salts (PQASs), chitosan, Polyethyleneimine (PEI), and its derivatives. The positive charge of the antimicrobial agent engages in an interaction with the negative charge present on the bacterial surface. This interaction subsequently results in the disruption of the bacterial cell membrane or the formation of the cell wall, leading to the release of cytoplasm and ultimately causing the death of the bacterium.

The generation of PQASs can be achieved *via* two methods: The polymerization of quaternary ammonium compounds at the small molecule level, or the quaternization of polymers. For example, Lv, et al. fabricated nanofiber membranes composed of

poly ([2-(Methacryloyloxy)-Ethyl] Trimethyl Ammonium Chloride (METAC)) through an *in situ* cross-linking polymerization process utilising PMETAC, 2,2′-Azobisisisobutyronitrile (AIBN) as the initiator, and N,N′-Methylenebisacrylamide (MBA) as the cross-linking agent [14]. The Nanofibrous Membranes (NFMs) that were coated with PMETAC demonstrated noteworthy antibacterial efficacy against both *E. coli* and *S. aureus*, exhibiting rates as high as 90 percent. The results of the experiment demonstrated that both *Escherichia coli* and *Staphylococcus aureus* exhibited an approximate mortality rate of 99% upon exposure to the NFM-6.

Chitosan is an inherently present polymer that exhibits exceptional qualities in terms of biocompatibility, biodegradability, and antimicrobial efficacy. Chitinase plays a pivotal role in the synthesis of chitosan. The composite coating material was developed by Min et al. through the combination of quaternary ammonium salt-modified chitosan (HACC) and Polyvinyl Alcohol (PVA) [15]. The application of the Hydrophobic Antimicrobial Coating Compound (HACC) yielded remarkable antibacterial characteristics to the treated surface, leading to a significant reduction in the viability of microorganisms, including *E. coli* and *S. aureus*, with a mortality rate of 99%.

Polyelectrolytes (PEIs) possess a wide array of antibacterial properties owing to their abundant positive charges and varied structures. The efficacy of cationic Polyethyleneimine (PEI) nanoparticles as antibacterial agents has been demonstrated through their ability to effectively bind to proteins and provide structural stabilization. Beyth et al. conducted *in vitro* biocompatibility investigations wherein they introduced cross-linked Quaternary Ammonium Polyethylene-Diamine (QPEI) nanoparticles into dental resin composites [16]. This integration yielded durable and extensive antibacterial properties, devoid of any observable adverse reactions.

**Photosensitive materials:** It is possible for photosensitive materials to produce cellular and microbial inactivation through a process that is known as Photodynamic Antimicrobial Chemotherapy (PACT). This process is carried out when photosensitive materials are employed in conjunction with photodynamic therapy. The process of photoactivation crosslinking and chain reaction, commonly referred to as PACT, is a mechanism of oxidative damage that relies on the coordinated interplay of three essential components: Light, a photosensitizer, and oxygen. After numerous iterations of differential passages, it is observed that the aforementioned method rarely leads to the development of bacterial resistance in either the original bacteria or its progeny. PACT has generated considerable attention in the realm of antimicrobial research due to its notable spatiotemporal selectivity, noninvasive characteristics, minimal occurrence of drug resistance, and applicability for localised infection treatment facilitated by the penetrating laser. In recent times, a novel antimicrobial approach known as Electroluminescent Power Therapy (ELPT) has been employed to generate Reactive Oxygen Species (ROS) within a specific location by means of an electric field. This implies that the fluorescence emitted by Electroluminescent (EL) molecules stimulated the photosensitizers, resulting in the generation of singlet oxygen and subsequent oxidative damage. The ELDT technology is founded upon the utilisation of nano-assemblies composed of Electroluminescent (EL) materials and photosensitizers. Zhang et al. devised a flexible therapeutic apparatus through the incorporation of hydrogel-loaded ELDT nanoparticles into its structure [17]. The ELDT-based flexible device has been found to exhibit a high level of antibacterial activity, reaching 99.9%, specifically targeting drug-resistant bacteria. This activity is achieved through the induction of Reactive Oxygen Species (ROS), resulting in bacterial cell death. The device shows potential for treating superficial infections and facilitating the healing process of wounds.

**Peptides with antimicrobial activity (AMPs):** When used for an extended period of time, traditional antibiotics with a single target are often more likely to develop resistance. Antimicrobial Peptides (AMPs) represent a distinctive alternative to conventional antibiotics, demonstrating potent broad-spectrum antimicrobial activity against a variety of Multidrug-Resistant (MDR) bacteria. The bactericidal multi-modal action mechanisms of Antimicrobial Peptides (AMPs) contribute to their unique properties, making them a highly appealing treatment option due to their slow or negligible development of resistance.

In the year 1980, a scholar from Switzerland by the name of G. Boman successfully isolated the initial animal Antimicrobial Peptide (AMP) cecropins from a chrysalis. Subsequently, a variety of antimicrobial peptides exhibiting antibacterial properties have been discovered, synthesised, and modified. In recent years, there has been a growing emphasis on Antimicrobial Peptide (AMP) research as a central aspect of combating bacterial resistance. Breij et al. conducted a study in which they generated and synthesised a collection of antibacterial and antibiofilm peptide SAAPs [18]. This was achieved by employing the human antimicrobial peptide LL-37 as the precursor peptide. The antimicrobial efficacy of these Synthetic Antimicrobial

Peptides (SAAPs) exhibited a significant enhancement compared to that of LL-37. The efficacy of SAAP-148 as an agent for eradicating Multidrug-Resistant bacteria (MDR bacteria), inhibiting biofilm formation, and eliminating pre-existing biofilms and persister cells has been demonstrated. Furthermore, Yue Fei and colleagues developed an Antimicrobial Peptide (AMP) known as FOTyr-AMP, drawing inspiration from the biofilm-disrupting capabilities and unique antibacterial properties of nitric oxide [19]. The synergistic interaction between nitric oxide and antimicrobial peptides led to the formation of a peptide that exhibited enhanced efficacy compared to cephalosporin C. This novel peptide demonstrated superior performance in effectively eradicating bacterial biofilms and exerting potent antibacterial effects.

Proline-Rich Antimicrobial Peptide (PrAMP) is considered a highly interesting candidate for targeted design against gram-negative bacteria due to its rapid mutation rate, low toxicity, and ability to interact with various intracellular targets. In their study, Li et al. conducted a series of chemical modifications on the proline-rich Antimicrobial Peptide (AMP) monomer Chex1-Arg20 [20]. The objective of these modifications was to enhance the antibacterial activity of the peptide against a wider range of bacterial strains. The researchers employed two bifunctional linkages, namely tetrafluorobenzene and octafluorobiphenyl, to facilitate the dimerization of Chex1-Arg20. This process led to a notable enhancement in the antibacterial activity of the compound. The dimeric peptide exhibited significant efficacy against gram-negative bacteria, with a notable emphasis on the multidrug-resistant *A. baumannii* strain listed by the World Health Organisation (WHO). The observed cytotoxicity of this peptide was minimal. Furthermore, a time-kill kinetic assay was conducted to assess the bactericidal activity of the dimeric peptide. The results indicated that the peptide exhibited rapid bactericidal effects and significantly reduced the formation of bacterial biofilm by over fifty percent. These findings are crucial in establishing fundamental parameters for future investigations in clinical pharmacokinetics and the development of therapeutic agents.

Due to their robust antimicrobial properties, broad spectrum of antimicrobial activity, substantial diversity, and reduced likelihood of resistance mutations in target strains, antimicrobial peptides (AMPs) possess numerous potential applications. Polymyxin and short bacillus peptide are two peptide antibacterial drugs now in clinical use. There are also a large number of patents on antimicrobial peptide sequences that have been shown to be effective. Despite extensive research, only a small fraction of AMPs are being employed in clinical practice. Most AMPs are currently in late-stage clinical trials, and there are many open questions about their use and manufacture. For instance, enzymes readily degrade antimicrobial peptides because of their peptide-like chemical structure. Natural antimicrobial peptides are scarce, and their extraction is a time-consuming and laborious process. Chemically synthesized peptides should think about the high cost and issues of industrialization.

### Controlling antibiotic resistance

Antibiotic resistance is a critical worldwide health hazard that occurs when bacteria gain the ability to withstand antibiotic actions, making them more difficult to treat. Antibiotic overuse and misuse both contribute to resistance development. This leads to longer and more severe diseases, more medical visits, the use of stronger and more expensive treatments, and even more bacterial infections-related deaths.

Individuals can prevent antibiotic resistance by taking basic precautions like as washing their hands often, getting vaccinated, and only taking antibiotics as prescribed by a healthcare practitioner. It is critical to recognize that antibiotics are ineffective against viral diseases such as colds and flu, and using them excessively can result in significant side effects and contribute to antibiotic resistance.

Healthcare workers can help tackle antibiotic resistance by providing antibiotics only when necessary and according to proper prescribing standards. It is critical in hospitals to use the CDC's dedicated network to limit the transmission of resistant bacteria among patients.

## CONCLUSION

Antibiotics have a two-edged sword. Antibiotic invention and application have been called "one of the greatest scientific and technological achievements of the twentieth century." Antibiotics, which work *via* a variety of bactericidal processes, have given humanity a potent tool in the battle against mortality, preventing the deaths of many people who might otherwise have succumbed to bacterial infections. Antibiotics have been a cornerstone of infection treatment for quite some time.

Nevertheless, the improper use of antibiotics has expedited the emergence of bacteria that are resistant to these drugs, thereby presenting a significant risk to the well-being of individuals. The widespread use of antibiotics and other antibacterial methods has resulted in the emergence of more complex resistance mechanisms, particularly the development of microorganisms that are resistant to multiple drugs. This calls for studies into both the antibiotics' bactericidal activity and the bacteria's resistance mechanism. Moreover, the development of materials science and pharmaceuticals has opened up various avenues for study. In the future, bacterial resistance may be overcome with the help of polymer materials, antibacterial peptides, and DDS technologies.

At the moment, most research is focused on discovering antibiotic alternatives. Antimicrobial materials are generally easy, however there are issues that must be addressed, such as metal nanomaterial metabolism and toxicity. Furthermore, antimicrobial substance elimination *in vivo* is always generally quick. Due to their nanoscale properties, Drug Delivery Systems (DDSs) have been developed with a range of benefits, such as prolonged circulation within the body, decreased drug toxicity, and enhanced drug targeting capabilities. These advantages have contributed to improved treatment efficacy. The primary constraint lies in the biosafety of the carriers, which concurrently serves as the most significant impediment to their integration into clinical investigations. Consequently, a thorough investigation is necessary in order to facilitate the industrialization and enhance the potential for application. Nevertheless, the presence of peptides in the market serves as a testament to our assurance that emerging technologies and scientific breakthroughs will be implemented in clinical settings to effectively address antimicrobial challenges in the foreseeable future.

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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