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Recent Advances in Antibiotics: Mechanisms, Clinical Manifestations, Opportunities, and Development

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ABSTRACT:

Antimicrobial resistance (AMR) is a major global health concern, largely driven by the excessive and improper use of antimicrobials in both medical and agricultural practices. Antibiotics are becoming increasingly popular due to their ability to promote tissue regeneration, antifungal activity, and antiviral activity. In this context, probiotics and microbiota management have emerged as promising tools to prevent infections and reduce reliance on antibiotics. This review aims to provide a brief overview of the mechanisms, brief clinical manifestations, opportunities and development. The main objective of this review is to provide an overview of antibacterial agents mechanisms and brief clinical features. The creation of new antibiotics is in progress to address the growing challenges posed by AMR. A particularly promising strategy in this field involves the creation of narrow-spectrum antibiotics: Ceftolozane-Tazobactam (Zerbaxa). Antibiotic peptides (AMPs) and peptidomimetics are gaining recognition as viable alternatives to conventional antibiotics, presenting novel strategies to combat the escalating issue of anti-AMR. ASPs can incorporate drug repurposing strategies to extend the lifespan of existing antibiotics Surveillance and Research: ASP can incorporate drugs repurposed drugs to provide immediate therapeutic options for multidrug-resistant (MDR) infections.

KEYWORDS: Antimicrobial resistance, Antibiotics, Multidrug-resistant, Gram-positive Bacteria, Narrow-spectrum.

INTRODUCTION :

Antimicrobial agents are compounds that can either destroy or slow down the growth of microorganisms such as bacteria, viruses, fungi, and parasites, all while minimizing any damage to the host These agents encompass antibiotics (which specifically target bacteria), antivirals, antifungals, and antiparasitic. They play a crucial role in managing infections in humans, animals, and plants. The effectiveness of these agents can be affected by various factors, such as the concentration of the drug, the type of microorganism involved, and the immune status of the host[1]. Antimicrobial resistance (AMR) has emerged as a significant global issue. Bacterial AMR occurs when bacteria evolve in ways that diminish the effectiveness of medications designed to combat infections, making it one of the foremost public health threats we face today. The Review on Antimicrobial Resistance, launched by the UK Government, cautioned that by 2050, AMR could lead to 10 million fatalities annually[2].While some have questioned these estimates, organizations like the WHO and numerous researchers concur that the growing issue of AMR demands a united global effort[3,4]. AMR represents a major threat to global human health [5,6]. Previous studies have examined the effects of AMR on incidence rates, mortality, hospitalizations, and healthcare costs associated with specific pathogen-drug combinations across various regions. To our knowledge, this research offers the most comprehensive estimates of AMR's impact to date[7,8].

Antimicrobial agents boast a history that stretches back more than 2000 years. Early civilizations, including the ancient Egyptians and Greeks, were among the first to utilize specific molds and plant extracts to fight infection [9]. In the 19th century, groundbreaking microbiologists such as Louis Pasteur and Jules Francois J'ouvert explored the competitive dynamics among different bacteria, aiming to harness these interactions for medical therapies [10]. Pasteur's groundbreaking work on fermentation and the concept of spontaneous generation led to a clearer

understanding of anaerobic and aerobic bacteria. His discoveries paved the way for Joseph Lister to implement antiseptic methods in surgery, including the sterilization of instruments and proper wound care. On September 3, 1928, a pivotal event took place when Alexander Fleming returned from his vacation to discover that a Petri dish containing Staphylococcus had been altered by the presence of the antimicrobial fungus Penicillium rubens. Initially facing challenges in isolating the antimicrobial agent, Fleming and his colleagues acknowledged its potential for therapeutic use, which they elaborated on in a publication from 1929 in the British Journal of Experimental Pathology [11].

Subsequently, in 1942, Howard Florey, Ernst Chain, and Edward Abraham built upon Fleming's research by purifying and extracting penicillin for medical purposes, a significant achievement that led to their receipt of the Nobel Prize in Medicine in 1945 [12]. The development of antibiotics is considered one of the key achievements of the 20th century. The use of substances to fight infections has a long history, dating back to ancient cultures that used various natural extracts for their healing properties. Many of these extracts, derived from plants and fungi, demonstrated antibacterial properties long before the term "antibiotics" was even introduced[13]. The concept was initially presented by American microbiologist Selman Waksman and his team, who successfully extracted chemical compounds from microorganisms that inhibited the growth of other microbes[14]. Fleming's discovery acted as an important bridge connecting ancient healing methods, like the Egyptians using mouldy bread to treat infections, to the contemporary age of antibiotics[15,16]. Following World War II, a period commonly known as the "golden era" of antibiotic discovery, numerous classes of antibiotics were created that continue to be used today[17]. The arrival of penicillin sparked a strong belief in the ability to effectively treat infections with antibiotics, even though sulphonamides were the first antimicrobials used and faced issues with resistance that still impact treatment today. Significant advancements occurred in the subsequent years, highlighted by the introduction of antibiotics including streptomycin, chloramphenicol, tetracyclines, erythromycin, vancomycin, and cephalosporins, among others. This increase in available antibiotics transformed previously fatal diseases into manageable health issues, signaling the onset of the antibiotic era[18,19]. Notably, antibiotics such as vancomycin have been essential in combating drug-resistant bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA).The significance of creating new antimicrobial agents cannot be overstated. The rapid increase in the application of antimicrobial therapies has allowed for a certain level of management of microbial-related diseases in humans. Nevertheless, the emergence of microbial resistance to antibiotics has developed concurrently, leading to a continuous struggle to produce newer agents that can combat these more resistant strains. Consequently, it is imperative for practicing clinicians to stay updated on contemporary antimicrobial agents and to comprehend their fundamental mechanisms of action. Over the past twenty years, there has been an extraordinary surge in the discovery and development of new antimicrobial agents. An overview of the wide range of new penicillin's, cephalosporins, and quinolones that were not accessible in 1965 reinforces the idea that this progress resulted from a variety of research and discovery efforts in multiple chemical fields. However, a more detailed examination of the history of antibiotic development reveals a more coordinated series of events, where the advancement of several structural classes of compounds was significantly interlinked. Advancements in our comprehension of bacterial physiology have enabled the development of structure-activity relationships (SAR). These relationships have played a crucial role in directing the chemical alterations of antibiotics to improve their effectiveness against bacteria. Furthermore, this approach has aided in the discovery of new antibiotics that are effective against strains that have become resistant to previously used treatments[20].

The urgent need for new antimicrobial agents is becoming more apparent as antimicrobial resistance (AMR) rises rapidly, jeopardizing the effectiveness of treatments for common infectious diseases. The World Health Organization (WHO) recognizes antimicrobial resistance (AMR) as a leading global health challenge that could reverse years of progress in medicine and public health. The inappropriate use and excessive reliance on antibiotics in human healthcare and agriculture play a major role in this problem, enabling pathogens to evolve and withstand existing treatments. Existing antimicrobial agents are increasingly challenged by evolving pathogens, resulting in a rising number of instances where conventional therapies fail. This situation underscores the urgent requirement for new antimicrobial agents that can not only bypass resistance mechanisms but also ideally engage novel biological pathways, thereby diminishing the likelihood of resistance emergence. The creation of these innovative agents is vital for safeguarding at-risk populations, such as individuals undergoing surgical procedures, cancer therapies, or organ transplants, who depend on antimicrobials to avert severe infections. In light of this challenge, it is imperative to invest in research and development, not only to formulate new antibiotics but also to establish rapid diagnostic tools and effective stewardship programs. These stewardship initiatives aim to optimize antibiotic usage, which can reduce selective pressure and help maintain the efficacy of new treatments. Without prompt action and a renewed commitment to research, there exists a significant risk of reverting to a time when common infections could once again pose life-threatening risks. Therefore, the advancement of new antimicrobial agents is not only a healthcare imperative but also a moral obligation to future generations[21].

OBJECTIVE AND SCOPE OF THE REVIEW:

The main objective of this review is to provide an overview of antimicrobial agent's mechanisms, brief clinical manifestations, opportunities and development.

MECHANISMS OF ACTION OF ANTIMICROBIAL ANGENTS:

Antimicrobial agents can be categorized into different groups according to how they work against microbes. The primary categories include agents that block cell wall formation, disrupt the cell membrane, hinder protein production, interfere with nucleic acid synthesis, and obstruct metabolic processes in bacteria. Table. 1 provides examples of medications from each of these categories. With such a diverse array of mechanisms, one might expect improved control over these organisms. Sadly, the misuse of antimicrobial agents has significantly contributed to the serious resistance problem we are currently encountering[22].

Table 1. Mechanism of action of antimicrobial agents

S.No	Mechanism Of Action	Antimicrobial Groups
1	Block the creation of the cell wall.	β-Lactams include various types of antibiotics like Carbapenems, Cephalosporins, Monobactams, Penicillin's, and Glycopeptides.
2	Depolarize Cell Membrane	
3	Block the production of proteins.	Aminoglycosides and tetracyclines attach to the 30S ribosomal subunit. On the other hand, chloramphenicol, lincosamides, and macrolides bind to the 50S ribosomal subunit, along with oxazolidinones and streptogramins.
4	Block the production of nucleic acids.	Quinolones-; Fluoroquinolones
5	Block Metabolic Processes.	Sulfonamides Trimethoprim

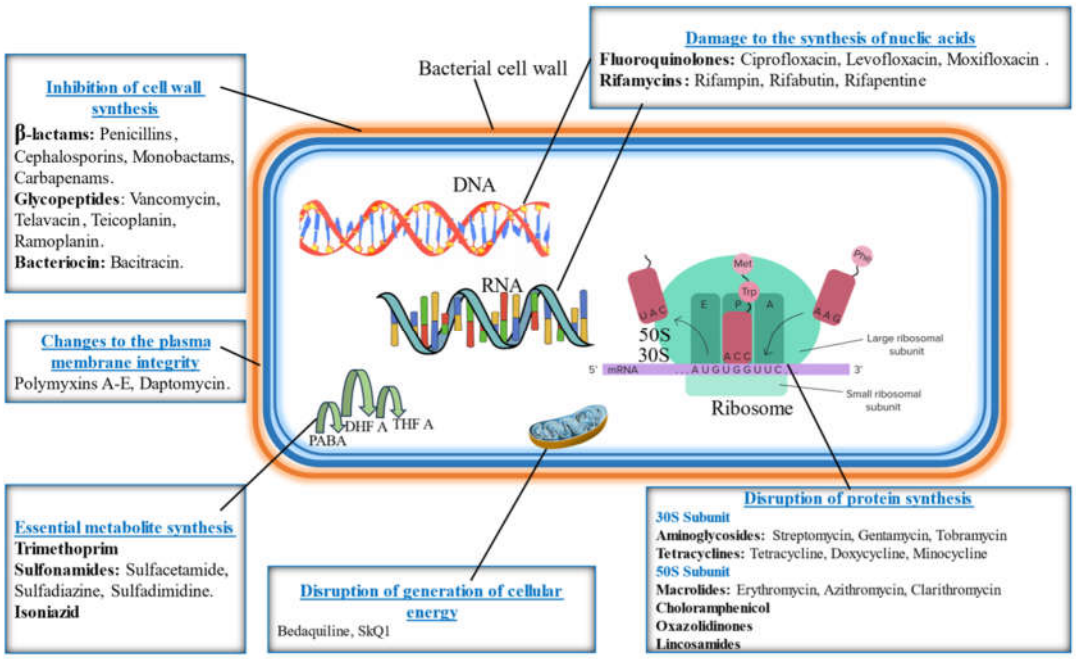


Figure 1. Mechanism of action of antimicrobial agents

Beta (β)-lactam antibiotics were among the earliest classes of antibacterial drugs created. This group includes a variety of antibiotics that all share a common feature: A β-lactam ring is present in their chemical structure. Key representatives of this class include penicillin derivatives (called penams), cephalosporins (known as cephems), monobactams, and carbapenems[23]. These antibiotics function as irreversible inhibitors of the enzyme transpeptidase, which is crucial for the formation of bacterial cell walls. The transpeptidation process, necessary for constructing peptidoglycan, is facilitated by transpeptidase, often known as penicillin-binding proteins (PBPs). Penicillin-binding proteins (PBPs) interact with the D-Ala-D-Ala terminus of muropeptides, which are essential

components of peptidoglycan, to facilitate crosslinking. B-lactam antibiotics mimic this binding site, thereby competitively obstructing the crosslinking activity of PBPs[24].

Aminoglycosides are crucial in treating infections caused by Gram-negative bacteria. They are highly effective against aerobic, Gram-negative strains and can work well in combination with some Gram-positive bacteria[25]. This group of antibiotics plays a crucial role in therapy, but their application is often restricted due to possible toxicity and the risk of residues in animals raised for food. Aminoglycosides are derived from various strains of Streptomyces spp., Micromonospora spp., and Bacillus spp. Prominent examples include neomycin, streptomycin, and kanamycin, with neomycin consisting of neomycin A and B. Additional significant members of this class are paromomycin and framycetin. These antibiotics function by inhibiting protein synthesis, as they bind to the 16S rRNA and disrupt the structural integrity of the bacterial cell membrane[26].

Table 2. Family of antimicrobial agents & its Mechanism of action.

Sr.no.	Antimicrobial family	Mechanism of action	Resistance mechanism
1	Beta-lactam antibiotics	Prevents the creation of cell walls by attaching to PBPs, the enzymes responsible for building peptidoglycans.	Beta-lactamase production mainly occurs in blagenes. It alters the cell wall protein enzymes, making it difficult for them to bind to PBPs.
2	Aminoglycosides	rRNA attaches to the 30S subunit, leading to errors in reading the genetic code. This disrupts protein synthesis and affects the permeability of the cell membrane. Modifications like phosphorylation, adenylation, and acetylation of aminoglycosides prevent them from binding effectively.	Aminoglycosides are prevented from binding when they undergo phosphorylation, adenylation, or acetylation.

CHALLENGES IN THE DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS (SCIENTIFIC CHALLENGES, RESISTANCES MECHANISM, MUTATION RATES, BIOFILM-ASSOCIATED RESISTANCE:

The creation of new antimicrobial agents encounters numerous scientific hurdles, especially concerning the resistance strategies that microorganisms utilize, their rates of mutation, and the impact of biofilms on resistance. Here are some of the main challenges. Microorganisms, including bacteria and fungi, have developed a range of resistance mechanisms against antimicrobial agents. These mechanisms can be grouped into different categories. For instance, many bacteria have developed efflux pumps that actively remove antimicrobial agents from the cell, thereby lowering their concentration and diminishing their effectiveness. Modifications to cellular targets in microorganisms can change the structure of these targets for antimicrobial drugs, such as altering enzymes or ribosomal subunits, which can render the drugs ineffective. One significant instance is the changes in penicillin-binding proteins (PBPs), which result in resistance to beta-lactam antibiotics. Moreover, some bacteria can generate enzymes that either break down or deactivate antimicrobial compounds. For instance, beta-lactamases are enzymes that can effectively dismantle beta-lactam antibiotics, rendering them ineffective. Additionally, certain pathogens might evolve alternative metabolic routes that bypass the blockage of crucial enzymes caused by antimicrobial drugs[27].

Mutation Rates and Evolutionary Pressure in microorganisms can rapidly evolve resistance due to their high mutation rates and short generation times. For example, bacteria can mutate to become resistant to antibiotics within a few generations, especially under selective pressure when exposed to suboptimal levels of antibiotics. The swift changes in microbial behavior pose a significant challenge to creating effective, long-lasting antimicrobial treatments. Moreover, horizontal gene transfer (HGT) facilitates the exchange of resistance genes among various species, which speeds up the dissemination of resistance even more. The high mutation rates in microorganisms contribute to the quick development of resistance[28]. Bacterial populations can quickly evolve through point mutations, which may lead to resistance against certain types of antibiotics. Biofilm-Associated Resistance refers to biofilms, which are groups of microorganisms surrounded by a self-produced extracellular matrix that stick to surfaces like medical devices, tissues, or natural environments. These biofilms create significant obstacles in the creation of antimicrobial agents. The extracellular matrix serves as a protective layer, which makes it hard for antibiotics to get through and access the microorganisms inside. Additionally, the microorganisms found in biofilms usually exist in a dormant or slow-growing state, which makes them less vulnerable to antibiotics that focus on active cellular processes. This phenomenon is referred to as “antibiotic tolerance”[29]. Furthermore, biofilms can modify the gene expression of microorganisms, which may enhance their resistance to various stressors, including antimicrobial agents and host immune responses. Moreover, within biofilms, microorganisms often display cooperative behavior, where resistant strains can provide protection to

sensitive strains, further complicating treatment approaches[30]. Intrinsic and Acquired Resistance Some microorganisms are inherently resistant to certain antimicrobial agents due to their natural characteristics, such as the lack of a target site for the drug or the presence of physical barriers (e.g., cell walls). Acquired Resistance is the type of resistance that arises due to mutations or the transfer of genes between organisms. When resistance genes are obtained, particularly from different species or even unrelated groups, it makes finding new effective treatments much more challenging.

Challenges in Drug Discovery and Development, the complexity of Targets in identifying new and specific targets for antimicrobial agents that are not easily bypassed by microbial resistance mechanisms is a significant challenge. Many targets already in use are rapidly overcome by microorganisms. The Toxicity and Side Effects of Developing antimicrobial agents with high specificity and minimal toxicity to human cells remains a key challenge. Many potential candidates fail due to adverse side effects. The development of novel antimicrobial agents requires significant investment in time and resources. The lengthy process of discovery, clinical trials, and approval makes it difficult for the pharmaceutical industry to justify the costs, particularly when antibiotics are often used for short durations and thus generate limited revenue. Impact of Combinations and Resistance Evolution, while combination therapies (using two or more drugs) may be an effective strategy to counteract resistance, they come with their own challenges, including the potential for synergistic resistance and the complexity of determining the best drug combinations. In environments with mixed microbial populations, resistance can evolve not just from direct drug exposure but also through indirect interactions (e.g., the exchange of resistance genes between different species)[31].

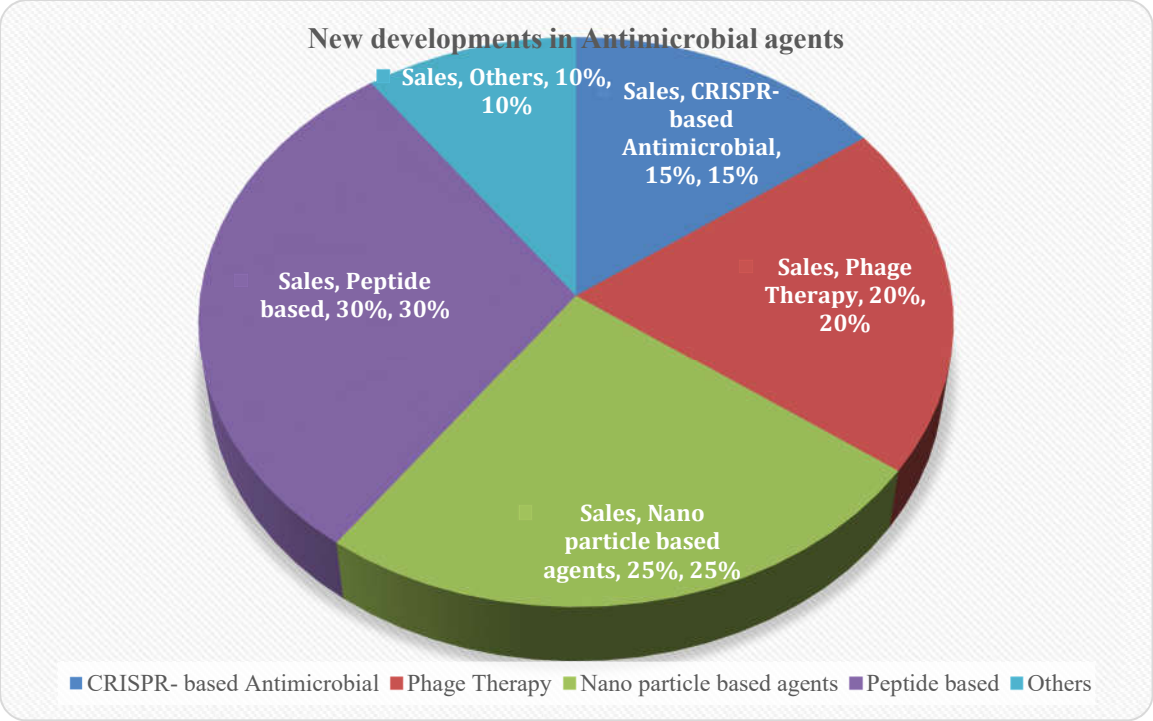


Figure 1. New developments in antimicrobial agents

The development of new antimicrobial agents faces significant challenges, particularly economic ones, such as the substantial costs involved in research and development. The R&D process for these agents can extend beyond ten years and necessitates considerable financial investment. Below are some of the primary economic obstacles encountered. Expensive Drug Discovery, identifying novel antimicrobial compounds involves screening thousands of potential candidates, most of which are not successful. This process is costly, requiring significant

investment in laboratories, technology, and skilled personnel. Research institutions, pharmaceutical companies, and biotech firms invest millions of dollars into preclinical and clinical development stages, with many failures along the way. Studies suggest the cost of developing a new antimicrobial can range from $800 million to over $1 billion. Development Timeline of Antimicrobial agents must undergo rigorous preclinical and clinical trials, including multiple phases of testing in human volunteers to ensure safety and efficacy. The long duration of development and multiple regulatory hurdles further add to the costs. Lack al Incentives, Low Profit Margins, Antimicrobials, particularly antibiotics, often have limited market potential. These drugs are used for short durations and sometimes only in severe cases, which does not generate high profits for manufacturers[31]. Additionally, the rise of generic alternatives reduces the potential for long-term profits after the patent expires. The economic return on investment is lower compared to drugs for chronic conditions like diabetes or heart disease, which can be prescribed for years. This has led to a lack of investment in antimicrobial R&D. Antimicrobial Ree increasing problem of antimicrobial resistance (AMR) complicates the situation. The more a drug is used, the more likely resistance develops, leading to decreased effectiveness. Therefore, newer antimicrobial agents may only be used sparingly to preserve their effectiveness, limiting their market potential and further discouraging investment. Regulatory Challenges for new drugs are long and expensive. Antimicrobial agents have to go through tough approval procedures established by regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[32]. This lengthy approval process increases the cost of development, especially for small pharmaceutical companies that might not have the financial resources to navigate complex regulatory landscapes. Price Controls and Market Access of antibiotics is controlled or heavily negotiated, which can further discourage investment by reducing potential returns for developers. Additionally, the global nature of the AMR crisis means that developing new antimicrobials that can be accessed by both high-income and low-income countries becomes a significant challenge, as price disparities may limit market access. Lack of Collaborative Efforts like Insufficient private Partnerships, Public-private partnerships (PPPs) have been seen as a potential way to reduce the financial burden of antimicrobial R&D. Collaborations in this field are still quite limited. While governments and international organizations like the World Health Organization (WHO) have taken steps to promote the development of new antimicrobials—such as through initiatives like the Global Antimicrobial Resistance and Use Surveillance System—these efforts have not been enough to overcome the economic challenges. The quest for new antimicrobial agents faces significant hurdles, mainly due to the lack of incentives for pharmaceutical companies to invest in antimicrobial research[33]. This issue is driven by several factors, including financial, market, and regulatory considerations. Low return on Investment (ROI), Short Duration of Use of Antimicrobials, especially antibiotics, are often used for short periods, typically to treat acute infections. This contrasts with medications for chronic conditions (e.g., diabetes or hypertension), which are used long-term, providing a consistent and high return on investment. The limited duration of antimicrobial use means that pharmaceutical companies may not see a substantial financial return on their investment in R&D. Price Pressure in many countries, antibiotics are subject to price controls, and reimbursement systems for antimicrobial drugs are often restrictive. This can limit the potential market price and overall profit, making them less attractive for investment compared to drugs with higher and more sustained profit margins. Antibiotics are prescribed only when necessary to treat bacterial infections, and their use is often restricted to avoid contributing to antimicrobial resistance (AMR). This limited demand reduces the potential market size for new antibiotics, making them less appealing to companies looking for profitable drugs with broad and frequent use. After the patent for an antimicrobial expires, generic versions can flood the market, often at a fraction of the price of the branded drug. This limits the revenue pharmaceutical companies can earn from new antibiotics, further decreasing their incentive to invest in developing new agents[34].

Antimicrobial Resistance (AMR), Short Lifespan Due to Resistance lead to rapid development of resistance to antibiotics means that new drugs often become ineffective relatively quickly, diminishing their market potential. As more resistant strains of bacteria evolve, newer antibiotics might be used less frequently to preserve their effectiveness, further limiting their sales. Incentive to Develop Drugs for a "Niche" Market, Companies might be reluctant to invest in developing antibiotics if the drugs will be used sparingly to delay resistance. Additionally, the growing global problem of AMR calls for a sustainable, strategic approach to antibiotic stewardship, which again means restricted use of these drugs. High Research and Development Costs & Expensive and Lengthy Process, The R&D process for new antibiotics is lengthy and costly, involving extensive preclinical and clinical trials. With high failure rates in early stages, the financial risks for pharmaceutical companies are substantial[35]. The high costs are difficult to justify when the long-term profitability of the drug is uncertain due to the aforementioned factors. Limited Public Funding While there are some public initiatives aimed at incentivizing antimicrobial development (such as government funding and public-private partnerships). These efforts are still

insufficient to offset the financial risks involved. Without guaranteed profits or sufficient funding, companies are less inclined to invest heavily in this area.

Regulatory and Market Access Challenges for new antibiotics is rigorous and time-consuming. This increases the cost of bringing a new antimicrobial agent to market and adds to the financial burden. Furthermore, the regulatory environment in some countries can complicate market entry, discouraging investment. The global nature of AMR means that companies must consider market access in both high-income and low-income countries. In low-income countries, the cost of new antibiotics may be prohibitive, further limiting market access and profitability. Risk of Low Adoption, the stewardship programs aimed at controlling AMR encourage the cautious use of antibiotics, which means that even new antibiotics are often reserved for severe or rare infections. This limits their widespread adoption and further reduces the incentive for companies to develop these drugs[36].

Emerging Antimicrobial Agents:

The creation of new antimicrobial agents is in progress to address the growing challenges posed by antimicrobial resistance (AMR). A particularly promising strategy in this field involves the creation of narrow-spectrum antibiotics. These medications are formulated to specifically target certain pathogens, thereby lessening the effect on the normal microbiota and decreasing the chances of resistance emergence. Narrow-spectrum antibiotics provide a more focused treatment option compared to broad-spectrum antibiotics, which target a wide range of bacteria. This targeted approach enables more precise treatment for specific infections. Reduced Disruption to Normal Microbiota, Broad-spectrum antibiotics often disrupt the balance of the microbiome, killing not only harmful bacteria but also beneficial ones. This can lead to complications like opportunistic infections (e.g., Clostridium difficile)[37]. Narrow-spectrum antibiotics target specific pathogens, helping to preserve the natural microbiota and reduce the risk of secondary infections. Reduced Selection Pressure for Resistance by targeting a narrower range of bacteria, these agents may reduce the evolutionary pressure on the broader microbial community, which can slow the development of resistance. Broad-spectrum antibiotics exert selection pressure on a wide variety of bacteria, promoting the development of resistant strains. Narrow-spectrum antibiotics can provide more targeted treatments for infections caused by specific pathogens, potentially improving the effectiveness of the therapy and reducing the risk of resistance[38]. Emerging Narrow-Spectrum Antibiotics: Ceftolozane-Tazobactam (Zerbaxa) Ceftolozane represents a novel cephalosporin that is paired with tazobactam, which functions as a beta-lactamase inhibitor. This antibiotic demonstrates efficacy against Pseudomonas aeruginosa and Escherichia coli, both of which are prevalent pathogens associated with hospital-acquired infections. One of its primary applications is for managing complicated urinary tract infections (cUTIs) and complicated infections within the abdominal area. This antibiotic is categorized as narrow-spectrum because it specifically targets certain Gram-negative bacteria. Fidaxomicin (Dificid) is a macrocyclic antibiotic that specifically targets Clostridium difficile (C. difficile), a bacterium that causes severe gastrointestinal infections. It has minimal effect on the normal gut microbiota, making it a good choice for C. difficile infections[39]. The treatment of C. difficile-associated diarrhoea (CDAD) is notably enhanced by the use of certain antibiotics, which are classified as narrow-spectrum due to their targeted action against this specific pathogen. Delafloxacin, also known as Baxdela, is a type of fluoroquinolone antibiotic that works well against many kinds of bacteria, including both Gram-positive and Gram-negative ones. It's mainly used to treat skin infections that are caused by tough bacteria, especially Staphylococcus aureus, which includes the resistant strain MRSA. This antibiotic is specifically meant for treating acute bacterial skin and skin structure infections (ABSSSI) caused by various germs. Its spectrum of activity is considered narrower than that of conventional fluoroquinolones, as it is particularly aimed at resistant strains. Narrow-spectrum β-lactam antibiotics, which include various penicillin derivatives like Nafcillin and Oxacillin, are effective in treating infections caused by specific Gram-positive bacteria, including Staphylococcus aureus and MRSA[40]. These agents are effective against a limited array of pathogens and have garnered attention in the face of antibiotic resistance due to their targeted action and relatively low propensity for promoting broader resistance.Narrow-spectrum antibiotics are less likely to be prescribed broadly, and in some cases, they may be used only when the specific pathogen is identified, which limits their market potential. This can make them less attractive to pharmaceutical companies. To effectively use narrow-spectrum antibiotics, precise diagnostics are needed to identify the specific pathogen. This requires access to advanced diagnostic tools, which can be a challenge in some healthcare settings[41]. Developing narrow-spectrum antibiotics involves significant R&D costs, and there is the challenge of balancing the cost of developing specialized drugs with the potential return on investment. The limited market size for specific pathogens can make these drugs less profitable compared to broad-spectrum agents.Emerging antimicrobial agents that utilize nanotechnology have attracted considerable interest due to their distinctive characteristics and their potential to combat the escalating issue of antimicrobial resistance (AMR). Antimicrobial agents based on nanotechnology, including silver nanoparticles (AgNPs) and quantum dots, have shown promising effectiveness against a diverse

array of pathogens, particularly those that are resistant to conventional drugs. Silver nanoparticles (AgNPs) are among the most extensively studied nanomaterials for antimicrobial purpose[42]. Their broad-spectrum antimicrobial properties stem from their capacity to interact with microbial cells, leading to structural damage and the disruption of essential cellular functions. Silver nanoparticles fight bacteria mainly by releasing silver ions (Ag+). These ions then interact with the membranes of bacterial cells, causing damage to the membranes and leading to the leakage of important substances from inside the cells. Interaction with Proteins and DNA can bind to bacterial proteins and DNA, disrupting cellular processes such as protein synthesis and replication. AgNPs generate reactive oxygen species, which can lead to oxidative stress and damage to cellular components. It's applications are Wound Dressings, Silver nanoparticles are commonly used in wound care products due to their ability to prevent infection and promote healing. For example, Acticoat, a wound dressing containing silver nanoparticles, has been widely used in clinical settings[43]. AgNPs are also used in water treatment to eliminate bacterial pathogens.Silver nanoparticle creams are being created to treat skin infections that are resistant to antibiotics, like Staphylococcus aureus, especially MRSA. Nano Silver is a commercially available product utilized in medical devices and wound care solutions, capitalizing on the antimicrobial characteristics of silver nanoparticles.

Quantum dots (QDs) are semiconductor nanocrystals distinguished by their unique optical and electronic properties. Although they are primarily investigated for imaging and diagnostic purposes, QDs also exhibit potential as antimicrobial agents. The surfaces of quantum dots can be modified with various coatings to enhance their interaction with bacterial cells. Like silver nanoparticles, QDs can produce reactive oxygen species that induce oxidative stress and result in bacterial cell death. Certain quantum dots, particularly those composed of metals such as cadmium or zinc, may release toxic ions, further contributing to their antimicrobial efficacy[44]. Coatings for Medical Devices: Quantum dots have been integrated into coatings medical devices, including catheters and implants, are designed to inhibit bacterial colonization and the formation of biofilms. Wound Healing, QDs are being explored for use in wound healing due to their antimicrobial properties and ability to promote tissue regeneration. Quantum dot-based materials can be applied to surfaces, such as textiles or plastics, to create antimicrobial coatings for healthcare settings[45]. CdSe/ZnS Quantum Dots have been utilized in various studies to exhibit antimicrobial properties against E. coli and Staphylococcus aureus. Their antimicrobial effect is enhanced when combined with light exposure, which further promotes ROS generation.

Other Nanomaterials with Antimicrobial Properties like silver nanoparticles, copper nanoparticles have been shown to have strong antimicrobial effects. Copper nanoparticles work similarly by generating ROS and disrupting bacterial membranes.Zinc Oxide Nanoparticles (ZnO) also possess antimicrobial activity, with applications in textiles and coatings for medical devices[46]. Their antibacterial properties are attributed to ROS production and interaction with bacterial cell structures.Nanotechnology-based antimicrobials have some cool advantages. One major benefit is that nanoparticles have a really large surface area compared to their volume. This allows them to interact with bacterial cells more effectively. Nanoparticles are small enough to penetrate bacterial biofilms and target pathogens that are otherwise resistant to conventional antibiotics. The multiple mechanisms of action (e.g., ROS generation, membrane disruption) make it difficult for bacteria to develop resistance compared to traditional antibiotics. Toxicity Concerns, while nanoparticles have shown efficacy against pathogens, their potential toxicity to human cells and the environment remains a concern. Toxicological studies are essential to determine safe dosages for medical and environmental use. The approval process for nanotechnology-based products is more complex due to the novel properties of nanoparticles, requiring extensive testing for safety and efficacy[47].

Antimicrobial peptides (AMPs) and peptidomimetics are gaining recognition as viable alternatives to conventional antibiotics, presenting novel strategies to address antimicrobial resistance (AMR). AMPs are peptides that are found in nature and are really important for the innate immune system in various living things, including humans. On the other hand, peptidomimetics are synthetic compounds designed to mimic the structure and function of AMPs, while providing improved stability and pharmacokinetic properties[48]. Antimicrobial Peptides (AMPs) are small, positively charged peptides known for their diverse antimicrobial effects. They can effectively target a variety of pathogens, such as bacteria, fungi, viruses, and some parasites. The mechanisms by which AMPs operate often involve disrupting microbial membranes, interfering with internal cellular processes, or blocking the attachment of microbes to host cells[49]. Antimicrobial peptides (AMPs) typically engage with and compromise the integrity of microbial cell membranes, resulting in the formation of pores or a reduction in membrane thickness, ultimately causing cell death. This system works really well against many kinds of bacteria, including both Gram-negative and Gram-positive ones, along with fungi[50]. Certain antimicrobial peptides (AMPs) possess the ability to traverse the microbial cell membrane, allowing them to reach intracellular elements such as DNA, RNA, or proteins. This interaction disrupts the cellular functions of the microorganism[51]. AMPs also have immunomodulatory effects, such as promoting wound healing, modulating inflammation, and enhancing host immune responses.Examples of Antimicrobial Peptides Defensins, these small peptides are found in various organisms, including humans, and are active against a wide range of pathogens. Human defensins (e.g., α-defensins and β-defensins) are critical components of the innate immune response. They bind to and disrupt

microbial membranes by forming pores, and they also have direct effects on the immune system, enhancing the body's defence mechanisms. LL-37, This peptide represents the sole human cathelicidin and demonstrates extensive activity against a variety of bacteria, fungi, and viruses. LL-37 is recognized for its capacity to eliminate pathogens through the disruption of their membranes, in addition to its role in modulating immune responses. Research has explored the use of LL-37 in topical formulations aimed at wound healing, as it facilitates tissue repair and helps to minimize the risk of infection. Initially identified in the skin of frogs, magainin's are known for their potent antimicrobial properties, which they achieve by creating pores in microbial membranes. Magainin 2 is one of the most studied peptides and has proven to be very effective against different types of pathogens, including both Gram-negative and Gram-positive bacteria[52]. Some AMPs can be toxic to human cells, particularly at higher concentrations.

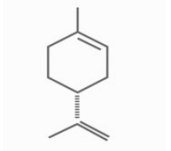
Stability: AMPs are often susceptible to proteolytic degradation, which limits their therapeutic potential. The production of natural AMPs in large quantities can be expensive, and their synthesis may be difficult due to their complex structures.Peptidomimetics are synthetic compounds designed to mimic the biological activity of peptides, including AMPs. They are typically more stable and easier to synthesize than natural peptides, making them attractive candidates for drug development.Mimicking AMP Activity: Peptidomimetics are designed to replicate the antimicrobial properties of natural peptides, such as disrupting microbial membranes or binding to bacterial enzymes. Peptidomimetics often incorporate non-peptide components to enhance their stability against enzymatic degradation, which is a common problem with natural peptides. By modifying the peptide backbone, peptidomimetics can be optimized to increase their antimicrobial activity while reducing toxicity to human cells. These are peptidomimetics that have been designed to mimic the structure of natural AMPs. One such compound, Melimine, is a synthetic mimetic of the human cathelicidin LL-37, showing promise in killing Staphylococcus aureus and other multidrug-resistant pathogens[53]. Melimine disrupts the bacterial cell membrane by inserting into lipid bilayers, creating pores, and leading to cell death.

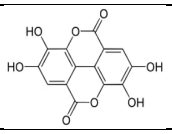
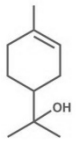
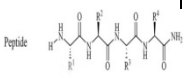
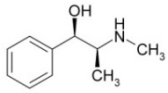
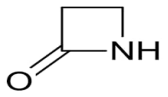
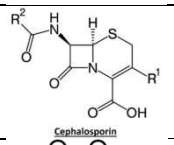
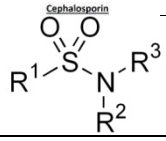
Applications: Melimine and other peptidomimetics have been explored for use in topical antimicrobial formulations, wound healing, and even as coatings for medical devices[54].
Synthetic Antimicrobial Peptides (SAMPs): These are synthetic analogs of natural peptides designed to enhance their antimicrobial properties. For example, D-Enantiomer Peptides have been engineered to resist enzymatic degradation and maintain potent antimicrobial activity against resistant bacteria.KLA peptides, a class of synthetic antimicrobial peptides, have been modified to mimic the amphipathic nature of natural AMPs while offering better stability and reduced toxicity[55]. Antimicrobial Peptoid Derivatives Peptoids are synthetic polymers that mimic peptides but with a modified backbone, making them more stable and resistant to proteases. These have shown broad-spectrum antimicrobial activity and can be designed to target specific bacterial strains. Peptoid-based antimicrobial agents have been developed to target E. coli and P. aeruginosa, offering an alternative to traditional antibiotics. Peptidomimetics are more stable than natural peptides, which makes them suitable for pharmaceutical development[56].
Reduced Toxicity: Through chemical modifications, peptidomimetics can be designed to minimize toxicity to human cells while retaining antimicrobial activity.
Target Specificity: Peptidomimetics can be fine-tuned to target specific bacterial pathogens or even bacterial virulence factors, offering more precise treatment options[57].

Challenges in the Development of AMPs and Peptidomimetics, Manufacturing and While peptidomimetics are generally easier and cheaper to produce than natural peptides, large-scale production still presents challenges[58]. Both natural AMPs and peptidomimetics can show toxicity to host cells, particularly at high concentrations[59]. Over time, bacteria may develop resistance to peptides, particularly if used frequently, although the complex mechanisms of action of AMPs make it less likely than for traditional antibiotics[60].

OPPORTUNITIES IN ANTIMICROBIAL DRUG DEVELOPMENT:

Table 3. Sources of antimicrobial agents.

S.no	Source	Component	Class	Compound	Structure	Other use	Ref.
1	Plant	Essential Oil	Terpenoids, Phenolics	Thymol, Carvacrol		Disrupt microbial cell membranes, inhibits enzyme activity.	[61]

		Phenolic	polyphenol	Flavonoid, tannins		Inhibits bacterial growth	61
2	Marine	Marine sponges	Natural product	Terpenoid, alkaloid		Affect microbial cell membrane integrity	62
		Oyster blood	Protein based	Lysozymes		Inhibit bacterial growth	62
3	Microbial source	Bacteria	Antibiotics	Alkaloids		Cell wall formation	63
		fungi	antibiotics	Beta lactam ring		Inhibits bacterial cel wall synthesis	64
4	Synthetic agents	Semi-synthetic	antibiotics	Cephalosporins		Block enzyme involved in bacterial replication	23
		Fully synthetic	antibiotics	Sulfonamide group		Inhibits folic acid synthesis	19

AI and ML in Antimicrobial Drug Discovery, Virtual Screening and Drug Design:
AI algorithms rapidly screen millions of compounds for antimicrobial activity, bypassing traditional trial-and-error methods. Example: Deep learning models predicting antimicrobial activity based on chemical structures. Generative models (e.g., GANs) create novel compounds optimized for antimicrobial properties. Target Identification and Validation, AI-powered analysis of genomic and proteomic data to identify novel bacterial targets[65]. Prediction of druggable targets using bioinformatics pipelines. Prediction of Resistance Mechanisms AI models forecasting the emergence of resistance based on pathogen mutation patterns and epidemiological data. Use of Big Data and High-Throughput Screening, Integration of big data from phenotypic assays, metagenomics, and high-throughput screening platforms. ML algorithms analyzing data from diverse sources to uncover potential antimicrobials. Advances in Natural Product Discovery Exploration of underutilized sources like soil metagenomes using AI. Revitalizing research into natural products, previously hindered by rediscovery of known molecules[66].

AI in Drug Repurposing:
Detecting currently available medications that may possess antimicrobial characteristics. Example: Use of AI to discover non-antibiotic drugs with antimicrobial activity (e.g., antimalarials effective against resistant bacteria). AI-Driven Pharmacokinetics and Pharmacodynamics, Use of ML to optimize dosage regimens by modelling pharmacokinetics (PK) and pharmacodynamics (PD)[67]. Predicting adverse effects and toxicity early in the drug development pipeline. Collaboration Between Academia, Industry, and Startups. Examples of AI-driven companies like Insilco Medicine and Atomise partnering with pharmaceutical firms. Open innovation platforms for collaborative data sharing. Challenges and Limitations. Data scarcity and quality issues. Computational cost of large-scale ML models[68].Ethical concerns around AI transparency. Future Directions Integration of AI with synthetic biology for antimicrobial peptide discovery[69]. Role of quantum computing in advancing ML algorithms for drug discovery.Policies promoting AI-driven research in AMR. Plant-Derived Natural Products are rich and historically significant source of bioactive compounds (e.g., alkaloids, terpenes, phenolics)[70].

Plant-Derived Antimicrobials: A Rich Source of Bioactive Compounds like Alkaloids: e.g., Berberine from Berberis vulgaris with broad-spectrum activity. Terpenoids: e.g., Artemisinin from Artemisia annua, active against resistant Plasmodium. Phenolic Compounds: e.g., Flavonoids with anti-inflammatory and antimicrobial

properties.Disruption of microbial membranes (e.g., essential oils from Eucalyptus).Inhibition of biofilm formation (e.g., extracts from Punicagranatum).Interference with microbial enzyme systems. Opportunities in Antimicrobial Drug Development Using Plant Extracts, Broad-Spectrum Activity Plant extracts effective against bacteria, fungi, and viruses[71]. Example: Tea tree oil (Melaleucaalternifolia) showing efficacy against Staphylococcus aureus and Candida albicans. Potential Against Resistant Pathogens Novel mechanisms bypassing traditional resistance pathways. Example: Garlic extract (Allium sativum) inhibiting multidrug-resistant Klebsiellapneumoniae. Synergistic Effects with Conventional Antibiotics. Enhanced activity when combined with synthetic antibiotics. Example: Curcumin (Curcuma longa) improving ciprofloxacin activity against E. coli. Sustainable and Renewable Sources Plants as a sustainable source compared to synthetic drugs[72]. Exploration of under-researched plant species from biodiversity hotspots. Advanced Extraction Techniques, Technologies like supercritical fluid extraction enhancing yield and purity. Recent Success Stories in Plant-Derived Antimicrobials. Neem (Azadirachtaindica): Active compounds like nimbidin against resistant bacteria[73].
Turmeric (Curcuma longa): Curcumin derivatives showing strong antibacterial and antifungal properties.
Cranberry (Vacciniummacrocarpon): Preventing urinary tract infections by inhibiting bacterial adhesion. Green Tea (Camellia sinensis): Epigallocatechingallate (EGCG) as a potent antimicrobial. Challenges and Limitations
Complexity of Plant Extracts:Mixture of compounds complicates standardization[74].Variability in Activity: Differences in plant growth conditions, harvesting, and preparation. Scalability Issues: Difficulty in producing sufficient quantities for clinical trials. Regulatory Hurdles: Lengthy approval process for natural product-based drugs. Future Directions, Integration with AI and Genomics: Identifying active compounds from plant libraries. Synthetic Biology: Engineering microbes to produce plant-derived antimicrobial compounds. Nanotechnology Applications: Enhancing bioavailability of plant-based antimicrobials. Global Collaboration: Harnessing ethnobotanical knowledge from diverse cultures[75].

Antimicrobial Stewardship and Drug Repurposing:

Antimicrobial resistance (AMR) is now a major global health concern, mainly driven by the overuse and misuse of antimicrobials in healthcare and farming. Antimicrobial stewardship programs (ASPs) are essential to combat this issue by optimizing antimicrobial use, preserving the efficacy of existing drugs, and improving patient outcomes. Drug repurposing—finding new uses for approved or investigational drugs—has become a valuable strategy in this context to address the declining pipeline of novel antimicrobials[76].The Significance of Antimicrobial Stewardship Programs (ASPs) lies in Maintaining Antimicrobial Effectiveness.Antimicrobial Stewardship Programs (ASPs) focus on using antibiotics wisely to prevent resistance from developing. By encouraging doctors to prescribe antibiotics correctly, they reduce the pressure on harmful bacteria, which in turn helps to slow down the rise of antibiotic resistance. Example: Restricting the use of broad-spectrum antibiotics like carbapenems in favor of narrower-spectrum agents whenever possible.Decrease in Resistance Rates Effective antibiotic stewardship programs (ASPs) have been associated with reduced rates of resistant infections[77]. Efforts aimed at encouraging the proper use of antibiotics have led to a decrease in infections from methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant Gram-negative bacteria. Cost Efficiency, ASPs can decrease healthcare costs by minimizing unnecessary antibiotic use and associated side effects, reducing hospital stays, and avoiding the need for expensive second-line therapies. Improved Patient Outcomes, Optimal antimicrobial use leads to better clinical outcomes, including faster recovery, fewer complications, and reduced mortality.

Drug Repurposing in Antimicrobial Stewardship: Filling the Antibiotic Development Gap, The development of novel antibiotics is a lengthy and expensive process[78]. Repurposing existing drugs offers a faster, cost-effective alternative to expand the antimicrobial arsenal.Example: The antifungal drug terbinafine has shown potential against certain bacterial pathogens like Mycobacterium tuberculosis.Combatting Multidrug Resistance, Repurposing drugs with known safety profiles can provide immediate therapeutic options for multidrug-resistant (MDR) infections.Example: The antimalarial drug chloroquine has shown antibacterial effects against resistant Escherichia coli[79]. Combination Therapies, Repurposed drugs can be combined with existing antibiotics to enhance efficacy or overcome resistance mechanisms.Example: Colistin combined with repurposed non-antibiotic drugs (e.g., statins) has demonstrated synergy against carbapenem-resistant Enterobacteriaceae.Host-Directed Therapies Some repurposed drugs target host mechanisms to enhance immune responses or reduce inflammation during infections. This approach helps avoid direct selective pressure on pathogens[80]. Synergy Between ASPs and Drug Repurposing ASPs can incorporate drug repurposing strategies to extend the lifespan of existing antibiotics Surveillance and Research: ASPs can monitor resistance trends to identify where repurposed drugs might be most effective. Education and Policy, Clinicians can be educated on evidence-based use of repurposed drugs within

stewardship frameworks. Guidelines Development, Updated treatment guidelines can integrate repurposed drugs where clinically validated.Challenges, Regulatory Barriers, Off-label use of repurposed drugs can face regulatory hurdles. Resistance Concerns, Overuse of repurposed drugs may also drive new resistance[81]. Economic Constraints, the lack of financial incentives for drug repurposing can limit its adoption.Antimicrobial resistance (AMR) has become a significant global health issue, largely fuelled by the excessive and improper use of antimicrobials in both medical and agricultural practices. Antimicrobial stewardship programs (ASPs) are essential to combat this issue by optimizing antimicrobial use, preserving the efficacy of existing drugs, and improving patient outcomes. Drug repurposing—finding new uses for approved or investigational drugs—has become a valuable strategy in this context to address the declining pipeline of novel antimicrobials[82].The significance of Antimicrobial Stewardship Programs (ASPs) lies in their role in maintaining the effectiveness of antimicrobials. These programs focus on using antibiotics wisely to prevent resistance from developing. By encouraging doctors to prescribe them correctly, they reduce the pressure on harmful bacteria, which helps slow down the rise of antibiotic resistance.Example: Restricting the use of broad-spectrum antibiotics like carbapenems in favor of narrower-spectrum agents whenever possible. Reduction in Resistance Rates Effective ASPs have been linked to lower rates of resistant infections. Initiatives aimed at encouraging the careful use of antibiotics have led to a decrease in infections caused by methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant Gram-negative bacteria. Cost Efficiency ASPs can decrease healthcare costs by minimizing unnecessary antibiotic use and associated side effects, reducing hospital stays, and avoiding the need for expensive second-line therapies[83].Improved Patient Outcomes, Optimal antimicrobial use leads to better clinical outcomes, including faster recovery, fewer complications, and reduced mortality.Drug Repurposing in Antimicrobial Stewardship, Filling the Antibiotic Development Gap, the development of novel antibiotics is a lengthy and expensive process. Repurposing existing drugs offers a faster, cost-effective alternative to expand the antimicrobial arsenal.Example: The antifungal drug terbinafine has shown potential against certain bacterial pathogens like Mycobacterium tuberculosis[84].Combatting Multidrug Resistance, Repurposing drugs with known safety profiles can provide immediate therapeutic options for multidrug-resistant (MDR) infections.Example: The antimalarial drug chloroquine has shown antibacterial effects against resistant Escherichia coli[85].Combination Therapies Repurposed drugs can be combined with existing antibiotics to enhance efficacy or overcome resistance mechanisms.Example: Colistin combined with repurposed non-antibiotic drugs (e.g., statins) has demonstrated synergy against carbapenem-resistant Enterobacteriaceae.Host-Directed Therapies, some repurposed drugs target host mechanisms to enhance immune responses or reduce inflammation during infections. This approach helps avoid direct selective pressure on pathogens[86].Synergy Between ASPs and Drug Repurposing ASPs can incorporate drug repurposing strategies to extend the lifespan of existing antibiotics Surveillance and Research: ASPs can monitor resistance trends to identify where repurposed drugs might be most effective. Education and Policy, Clinicians can be educated on evidence-based use of repurposed drugs within stewardship frameworks. Guidelines Development, Updated treatment guidelines can integrate repurposed drugs where clinically validated. Challenges Regulatory Barriers: Off-label use of repurposed drugs can face regulatory hurdles.Resistance Concerns: Overuse of repurposed drugs may also drive new resistance.

Economic Constraints: The lack of financial incentives for drug repurposing can limit its adoption. Conclusion, Antimicrobial stewardship programs are indispensable for preserving the efficacy of existing drugs, reducing resistance, and improving patient care. Integrating drug repurposing into ASPs offers a promising avenue to address the AMR crisis by expanding treatment options and complementing efforts to optimize antimicrobial use[87].Antimicrobial stewardship focuses on optimizing the use of antimicrobials to combat resistance, while drug repurposing explores new therapeutic applications for existing medications. Within this context, probiotics and microbiota management have emerged as promising tools to prevent infections and reduce reliance on antibiotics. Probiotics are beneficial live microbes that can enhance the health of the host when consumed in adequate amounts. They are essential for preserving gut balance and improving immune response. Certain strains of Lactobacillus and Bifidobacterium have shown effectiveness in preventing the colonization of harmful pathogens by producing bacteriocins, competing for essential nutrients, and reinforcing the intestinal barrier.Manipulating the microbiota through dietary interventions or fecal microbiota transplantation (FMT) has shown potential in restoring microbial diversity disrupted by antibiotics. Such strategies may prevent the overgrowth of antibiotic-resistant pathogens, such as Clostridioides difficile. By promoting a balanced microbiota, these approaches can indirectly reduce the demand for antibiotics and lower the risk of infection-related complications[88].Emerging research also suggests that probiotics may modulate systemic immune responses, thus providing protection against respiratory and urinary tract infections. For instance, randomized controlled trials have indicated that regular probiotic use decreases the incidence and severity of these infections, leading to a reduction in antibiotic prescriptions. By incorporating probiotics into clinical practice, antimicrobial stewardship programs can align with the principles of drug repurposing, utilizing microbiota-focused therapies as adjuncts or alternatives to conventional antimicrobials.

Regulatory and Policy Interventions:

Antimicrobial resistance (AMR) is a major danger to public health around the globe, making it essential to implement thorough regulations and policies. One key effort in this area is the Global Action Plan on AMR created by the World Health Organization, which was put into action in 2015. This plan advocates for a multi-faceted strategy to address resistance, emphasizing the importance of enhancing awareness, bolstering surveillance, decreasing infection rates, and promoting the responsible use of antimicrobials. Additionally, it highlights the need for investment in the development of new medications, diagnostic tools, and vaccines to combat AMR effectively. Countries have been encouraged to formulate national action plans that align with this framework, and numerous nations have enacted policies aimed at regulating antibiotic usage across human health, veterinary practices, and agricultural sectors. Nevertheless, the ongoing disparity in resource distribution and policy implementation between developed and developing countries continues to impede global advancements in this critical area[64].To stimulate the development of new antimicrobial drugs, incentive models like push and pull mechanisms have been introduced. Push incentives reduce the upfront costs of research and development (R&D) through grants, subsidies, and infrastructure support, allowing pharmaceutical companies to focus on innovation without immediate financial strain. On the other hand, pull incentives provide rewards for successful drug development, such as market entry rewards or advance purchase commitments, ensuring long-term profitability for effective drugs. For instance, the AMR Action Fund, launched in 2020, aims to invest over $1 billion to bring new antibiotics to market by 2030, exemplifying the potential of such models in addressing the antibiotic pipeline crisis. However, these incentives need to be scaled up and tailored to overcome the financial and scientific challenges associated with antimicrobial development. Addressing antimicrobial resistance (AMR) requires the harmonization of regulatory frameworks across borders to ensure the responsible use of antimicrobials. Many countries have put strict rules in place, such as restrictions on buying antibiotics without a prescription, mandatory prescriptions for their use, and monitoring how they are used in farming. The European Union (EU) has created detailed policies as part of its “One Health” initiative, which recognizes the links between human health, animal health, and the health of our environment. One major action the EU took was banning the use of antimicrobials as growth promoters in livestock in 2006. This decision has encouraged other countries to think about making similar rules. On the other hand, low- and middle-income countries (LMICs) struggle to put these kinds of policies into practice because they often lack resources, have informal healthcare systems, and face issues with public awareness. Addressing this regulatory disparity necessitates technical support, capacity enhancement, and international cooperation. Public-private partnerships (PPPs) are crucial in tackling the market failures associated with antimicrobial drug development. By combining resources, expertise, and funding from governments, international organizations, and private entities, PPPs facilitate collaborative innovation. The European Union (EU) has created detailed policies as part of its “One Health” initiative, recognizing how human, animal, and environmental health are all linked together. In 2006, the EU took a major step by prohibiting the use of antimicrobials to boost growth in livestock, which encouraged other countries to think about doing the same. However, low- and middle-income countries (LMICs) struggle to put these rules into practice because they often lack resources, have informal healthcare systems, and don’t have enough awareness about the issue.

These collaborations bridge the gap between discovery and commercialization, fostering a sustainable ecosystem for antimicrobial innovation. However, the success of PPPs hinges on transparent governance, equitable sharing of risks and benefits, and sustained political commitment. Public-private partnerships (PPPs) continue to evolve as critical vehicles for advancing antimicrobial drug development. Programs such as CARB-X and the Global Antibiotic Research and Development Partnership (GARDP) demonstrate how public-private partnerships (PPPs) can successfully address neglected pathogens while focusing on the needs of at-risk communities. By utilizing public funding alongside the expertise of the private sector, GARDP has successfully progressed multiple antibiotic candidates through clinical trials, addressing gaps that market-driven research and development often overlook. The involvement of philanthropic entities, including the Welcome Trust and the Bill & Melinda Gates Foundation, enhances the financial viability of these partnerships. Nevertheless, the effectiveness of such collaborations hinges on the ability to harmonize priorities among various stakeholders, including researchers, policymakers, and industry leaders, in order to reconcile public health objectives with commercial considerations[89].

FUTURE DIRECTIONS AND PERSPECTIVES:

The importance of interdisciplinary cooperation in tackling the worldwide problem of antimicrobial resistance (AMR) has grown. Combining expertise from microbiology, pharmacology, bioinformatics, and public health can facilitate the discovery of novel targets and innovative therapeutic strategies. For instance, integrating computational models with laboratory research can accelerate drug discovery, while insights from behavioral sciences can enhance public health interventions to curb misuse of antimicrobials. Such collaborative approaches

are critical to developing holistic and sustainable solutions to combat AMR effectively (Ventola, 2015). Advancements in drug development and delivery systems also hold great promise for tackling AMR. Innovations such as nanoparticle-based delivery, bacteriophage therapy, and CRISPR-Cas technologies are being explored to target resistant pathogens more precisely while minimizing collateral damage to healthy microbiota. Additionally, the use of artificial intelligence (AI) in identifying potential drug candidates and optimizing delivery mechanisms could significantly shorten the timeline for bringing effective antimicrobials to market (Martens &Demain, 2017)[90]. Personalized medicine offers a transformative approach to managing AMR by tailoring treatments to individual patients based on their genetic makeup, microbiome profile, and infection characteristics. Such precision strategies could reduce the overuse of broad-spectrum antibiotics and improve therapeutic outcomes. Diagnostic advancements, such as rapid genome sequencing, enable healthcare providers to match specific antimicrobials with pathogens more accurately, thus mitigating the risk of resistance development (O'Neill, 2016). However, the use of emerging antimicrobial agents raises several ethical concerns. Issues such as equitable access to new treatments, potential environmental impacts of novel drugs, and the implications of altering microbial ecosystems need to be addressed. Additionally, transparent regulation and monitoring are essential to ensure that innovations are deployed responsibly, avoiding unintended consequences that could exacerbate resistance problems in the long term (Littmann&Viens, 2015). The future of antimicrobial research is heavily reliant on integrating cutting-edge technologies to outpace the evolution of resistant pathogens. One such avenue is synthetic biology, which allows for the creation of customized antimicrobial compounds and optimized metabolic pathways for drug production. This approach, coupled with advanced high-throughput screening methods, can expedite the discovery of potent antimicrobial agents. Furthermore, innovations in metabolomics and proteomics provide insights into pathogen-host interactions, unveiling new targets for therapeutic interventions (de la Fuente-Núñez et al., 2017). Alternative therapies, such as antimicrobial peptides (AMPs) and bacteriocins, are gaining attention as promising substitutes for traditional antibiotics. These molecules exhibit unique mechanisms of action, such as disrupting microbial membranes, which make it harder for pathogens to develop resistance. Similarly, probiotics and microbiome-modulating strategies are emerging as non-conventional approaches to restore microbial balance and combat infections, particularly in cases where antibiotic use has caused dysbiosis (Ramakrishna et al., 2019)[61]. It is impossible to overestimate the importance of public knowledge and policy in combating antibiotic resistance. To impose more stringent laws on the use of antibiotics in healthcare and agriculture, governments and international organizations must cooperate. Campaigns for public education are also necessary to emphasize the risks of self-medication and encourage the proper use of antibiotics. Encouraging global collaborations such as the Global Antibiotic Research and Development Partnership (GARDP) can boost research efforts and ensure that treatments are accessible to everyone (World Health Organization, 2020). Economic factors are essential in determining how antimicrobial innovation will develop in the future. Despite the high societal cost of AMR, the pharmaceutical industry faces challenges in generating adequate returns on investment for new antimicrobial agents due to their restricted and targeted use. To address this, novel funding models, such as public-private partnerships, incentive mechanisms, and subscription-based payment models, are being developed to de-risk investments and encourage sustained research efforts in this field (Outterson et al., 2016)[62].

CONCLUSION:

Due to the extensive abuse and overuse of antibiotics as well as the declining supply of novel antimicrobial medicines, antimicrobial resistance (AMR) is a serious worldwide concern. The historical development of antimicrobial agents marked a revolution in medical science, saving millions of lives. However, the pace of resistance has far outstripped the innovation of new drugs, necessitating a collective and urgent effort to address this growing challenge. The development of novel antimicrobials and alternative therapeutic approaches is not only a scientific imperative but also a societal one, ensuring the sustainability of modern healthcare systems.Understanding the mechanisms of action of both traditional and novel antimicrobial agents is pivotal to designing next-generation therapies. Advances targeting bacterial biofilms, efflux pumps, and quorum sensing are promising, as are innovative approaches like bacteriophage therapy and antimicrobial peptides. These findings highlight how crucial it is to combine different fields of study in order to address the challenges posed by conventional antibiotics.

Despite these advancements, the development of new antimicrobial agents faces numerous challenges. Scientific barriers, such as biofilm-associated resistance and high mutation rates, complicate drug discovery. Economic and regulatory hurdles, including the high cost of R&D and stringent approval processes, deter pharmaceutical investment in this field. Addressing these issues requires targeted incentives, streamlined regulatory pathways, and sustained public-private partnerships. Emerging technologies hold immense potential for combating AMR. Narrow-spectrum antibiotics, nanotechnology-based antimicrobials, and synthetic biology approaches, such as CRISPR-Cas systems, exemplify the innovative strategies being explored. Additionally, antimicrobial peptides and peptidomimetics offer novel solutions to resistant infections. These advancements are complemented by opportunities in drug discovery, such as artificial intelligence, natural product-derived antimicrobials, and

synergistic combination therapies. Host-targeted therapies further expand the therapeutic landscape by leveraging the immune system to combat infections. Equally critical is the role of antimicrobial stewardship and drug repurposing. Stewardship programs are essential to preserve the efficacy of existing antibiotics, while repurposing non-antibiotic drugs and employing probiotics or microbiota management offer practical, cost-effective solutions to mitigate resistance. These efforts must be supported by robust regulatory and policy interventions, including global initiatives like the WHO's Global Action Plan and incentive models to stimulate pharmaceutical innovation.

Looking ahead, the future of AMR research lies in interdisciplinary collaboration, integrating expertise from microbiology, pharmacology, nanotechnology, and computational biology. Breakthroughs in drug development and delivery systems, personalized medicine, and ethical considerations in deploying emerging therapies will shape the trajectory of AMR management. In order to tackle antimicrobial resistance and ensure a better future for future generations, we must prioritize innovation, cooperation, and responsible stewardship.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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