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ANTIBIOTICS AND THEIR ACTION MECHANISMS

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Abstracts: Microorganisms are the primary natural source of antibiotics, with bacteria being the most prolific producers. In addition to bacteria, several other microbial groups—including fungi and actinomycetes—synthesize diverse antibiotic compounds that are widely applied in human and veterinary medicine as well as in agriculture. These bioactive molecules function as chemical defense tools, enabling microorganisms to compete with neighboring species in shared habitats. During the peak period of antibiotic discovery, often referred to as the "golden age," nearly 70–80% of identified antibiotics originated from a single bacterial genus, Streptomyces. One notable example is rapamycin, a compound produced by Streptomyces species that inhibits the growth of competing soil fungi. Beyond its ecological role, rapamycin has significant clinical applications as an immunosuppressive agent, particularly in preventing graft rejection following organ transplantation.Soil ecosystems harbor an exceptionally rich and diverse microbial community due to their complex and heterogeneous composition. Historically, soil-derived microorganisms have served as the cornerstone for antibiotic discovery and continue to be a vital resource for identifying novel antimicrobial compounds. However, the widespread and often unregulated use of antibiotics and disinfectants in healthcare, agriculture, and aquaculture has contributed to the alarming rise of multidrug-resistant pathogens. This growing resistance crisis underscores the urgent need to discover new and effective antimicrobial metabolites capable of combating resistant strains. In this context, soil microorganisms remain one of the most promising reservoirs for future antibiotic development. Antibiotic resistance has emerged as a major global public health concern. Importantly, resistance genes are not restricted to clinical settings but are also extensively distributed among environmental bacterial communities. This review discusses the major classes of antibiotics, their mechanisms of action, and the adverse effects associated with their misuse. Additionally, it examines the historical development of antibiotics, evaluates current challenges, and explores future prospects in antimicrobial research.

Keywords: Antibiotics, Squalamine, Soil microorganisms, Actinomycetes, Immunosuppressants, Antimicrobial activity

INTRODUCTION

The concept of "antibiotic" in microbiology originated from the French terms *antibiose* and *antibiotique*, which were introduced by Vuillemin in the late nineteenth century to describe substances capable of exerting harmful effects on living organisms. This definition was later broadened in 1947 when Selman A. Waksman described antibiotics as biologically active chemical compounds synthesized by microorganisms that can suppress the growth of or eliminate bacteria and other microbial species. Since their discovery, antibiotics have been extensively utilized in multiple fields, including human medicine, agriculture, animal husbandry, and aquaculture. Their antimicrobial effectiveness is primarily attributed to four major mechanisms of action: disruption of DNA replication, inhibition of protein synthesis, interference with cell wall formation, and blockage of folic acid metabolic pathways. Despite their widespread benefits, the rapid development and spread of antibiotic resistance has emerged as a serious and pressing global health challenge.

ANTIBIOTICS

An antibiotic is defined as a chemical compound synthesized by microorganisms that suppresses the growth of or destroys other microbial species. In contrast, an antimicrobial agent refers more broadly to substances obtained from natural biological sources or generated through chemical synthesis that inhibit or eliminate microorganisms. The term "antibiotic" was first introduced in 1942 by the soil microbiologist Dr. Selman A. Waksman, whose research, along with that of his collaborators, led to the discovery of numerous antibiotics derived from actinomycetes. Although antibiotics and antimicrobial agents differ slightly in definition, the terms are often used interchangeably in scientific literature, a convention that is also followed in this review. Accordingly, the term "antibiotic" is used here to denote any biologically derived or synthetically produced compound capable of inhibiting microbial growth or eradicating microorganisms to treat infections.

CLASSIFICATION OF ANTIBIOTICS

Antibiotics are generally categorized according to their mode of action, chemical composition, or range of antimicrobial activity. The majority exert their effects by disrupting essential bacterial structures or metabolic pathways required for growth and survival. Agents that interfere with cell wall synthesis, such as penicillins and cephalosporins, or compromise the integrity of the bacterial cell membrane, including polymyxins, typically display bactericidal properties, resulting in bacterial cell death. Similarly, antibiotics that inhibit critical bacterial enzymes—such as rifamycins, lipiarmycins, quinolones, and sulfonamides—also act in a bactericidal manner. In contrast, compounds that block protein biosynthesis, including macrolides, lincosamides, and tetracyclines, are primarily bacteriostatic, as they prevent bacterial proliferation rather than directly killing the cells.

Antibiotics may also be classified based on their spectrum of activity. Narrow-spectrum agents are effective against a limited group of bacteria, often targeting either Gram-positive or Gram-negative organisms, whereas broad-spectrum antibiotics act against a diverse range of bacterial species. Since antibiotics do not share a uniform mode of action, they are commonly grouped into major categories based on both their biochemical targets and chemical structures, which collectively define the four principal mechanisms of antibacterial activity.

A. Antibiotics inhibit DNA replication

All DNA polymerases responsible for bacterial genome replication are members of the C-family of DNA polymerases, a group that is largely restricted to bacteria. In contrast, the enzymes that carry out DNA replication in eukaryotic organisms belong to the B-family of DNA polymerases. A key structural distinction between these two families lies in the organization of the palm domain, which houses the catalytic residues essential for polymerase activity. In C-family polymerases, the palm domain is composed of a five-stranded β-sheet consisting of two parallel and three antiparallel strands, whereas B-family polymerases possess a palm domain formed by a four-stranded antiparallel β-sheet. Additionally, the amino acid residues constituting the catalytic triad are positioned on opposite faces of the β-sheet in these polymerases.

The fingers domain of C-family polymerases, which engages with the incoming nucleotide template and downstream DNA, is approximately twice the size of that found in B-family polymerases. This domain is followed by a C-terminal extension of roughly 100–150 amino acids that mediates interactions with the β sliding clamp and the τ (tau) subunit of the clamp-loading complex. Furthermore, C-family DNA polymerases contain an N-terminal

Polymerase and Histidinol Phosphatase (PHP) domain, a feature that is characteristic of bacterial polymerases and is present in only a limited number of fungal species.

Quinolones represent an important class of antimicrobial agents that disrupt DNA replication by targeting bacterial topoisomerases, most commonly topoisomerase II, also known as DNA gyrase. DNA gyrase plays a critical role in relieving supercoiling during DNA replication by introducing transient double-strand breaks and resealing phosphodiester bonds within closed circular DNA molecules. This process enables the progression of DNA and RNA polymerases along the DNA template. Fluoroquinolones, a second-generation subgroup of quinolones that includes ciprofloxacin, norfloxacin, and levofloxacin, exhibit broad activity against both Gram-positive and Gram-negative bacteria. Although topoisomerases are present in both prokaryotic and eukaryotic cells, quinolones selectively inhibit the bacterial form of topoisomerase II. In contrast, compounds that target mammalian topoisomerases, such as etoposide and irinotecan, are primarily employed as anticancer agents due to their ability to induce cytotoxic effects in rapidly dividing tumor cells.

B. Antibiotics inhibit cell wall synthesis

The majority of bacteria consist of a cytoplasmic membrane surrounded by a rigid cell wall, and in some species this structure is further enclosed by an additional outer layer. The bacterial cell wall performs essential functions, including maintaining cellular shape and protecting the cell from osmotic rupture caused by fluid influx. Certain classes of antimicrobial agents exert their effects by disrupting or inhibiting the synthesis of the bacterial cell wall. Because animal cells lack cell walls, this structure represents an ideal selective target for antibiotic action. A key component of the bacterial cell wall is peptidoglycan, which provides mechanical strength and structural stability, forming the primary and outermost framework of the cell wall.

The first class of antimicrobial drugs

Antimicrobial agents that disrupt bacterial cell wall formation primarily belong to the β-lactam class of antibiotics, which are defined by the presence of a β-lactam ring within their chemical structure. This group encompasses penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems. β-Lactam antibiotics exert bactericidal effects by blocking the synthesis of peptidoglycan, an essential structural component of the bacterial cell wall. The terminal stages of peptidoglycan assembly are mediated by enzymes known as penicillin-binding proteins (PBPs), which differ among bacterial species in their binding affinity for various β-lactam agents. A common mechanism of resistance to β-lactam antibiotics involves the production of β-lactamase enzymes, which deactivate the drug by cleaving the β-lactam ring. To counteract this resistance, β-lactam antibiotics are frequently co-administered with β-lactamase inhibitors, such as clavulanic acid.

Penicillins represent a major subgroup within the β-lactam antibiotics. Most penicillins, including penicillin G (benzylpenicillin), are derived from 6-aminopenicillanic acid and differ structurally based on substitutions at the side chain attached to the amino group. The β-lactam ring is the key structural element responsible for antimicrobial activity. Resistance to penicillins commonly arises from bacterial production of penicillinases (a type of β-lactamase), which hydrolyze the β-lactam ring and render the drug ineffective. Structurally, penicillins act as analogs of the D-alanyl-D-alanine dipeptide and competitively inhibit the transpeptidase enzyme involved in cross-linking peptidoglycan strands during cell wall synthesis. This inhibition weakens the cell wall, increases intracellular osmotic pressure, and ultimately results in bacterial cell lysis.

Naturally occurring penicillins, such as penicillin G and penicillin V, are particularly effective against susceptible Gram-positive cocci, including many streptococcal species, as well as certain Gram-negative organisms like meningococci and the causative agent of syphilis. Semi-synthetic penicillins, including ampicillin, amoxicillin, and carbenicillin, exhibit an expanded spectrum of activity and are useful in treating infections caused by Gram-negative enteric bacteria. Penicillinase-resistant penicillins, such as methicillin, nafcillin, and cloxacillin, are employed against infections involving penicillinase-producing strains. Overall, penicillins are generally well tolerated due to their selective action on bacterial cell walls, which are absent in human cells. However, clinical use is occasionally limited by allergic reactions and the increasing prevalence of resistant bacterial strains.

The second class of antimicrobial drugs

Glycopeptide antibiotics constitute an important group of antimicrobial agents that inhibit bacterial cell wall synthesis. These compounds are characterized by glycosylated cyclic or polycyclic

nonribosomally synthesized peptide structures. Notable members of this class include vancomycin, teicoplanin, telavancin, ramoplanin, decaplanin, and bleomycin. Glycopeptides exert their antibacterial activity primarily by interfering with the assembly of the peptidoglycan layer, which is essential for maintaining cell wall integrity in susceptible bacteria.

Vancomycin is one of the most clinically significant glycopeptide antibiotics and is produced by *Streptomyces orientalis*. Structurally, it consists of a peptide core attached to a disaccharide moiety, forming a distinctive cup-shaped configuration. Vancomycin inhibits cell wall synthesis by specifically binding to the terminal D-alanyl–D-alanine sequence of the pentapeptide side chains within peptidoglycan, thereby preventing the transpeptidation step required for cross-linking. This mechanism results in bactericidal activity against a range of Gram-positive organisms, including *Staphylococcus* species and selected members of the genera *Clostridium* (associated with gas gangrene), *Bacillus* (foodborne illness), *Streptococcus* (streptococcal pharyngitis), and *Enterococcus* (urinary tract infections).

Despite its clinical importance, the emergence of vancomycin-resistant strains, particularly among *Enterococcus* species and, more recently, *Staphylococcus aureus*, has become a major concern. Resistance typically arises from alterations in the peptidoglycan precursor, where the terminal D-alanine residue is replaced by D-lactate or D-serine, reducing the binding affinity of vancomycin for its target. The spread of vancomycin resistance represents a serious public health challenge, as this antibiotic has long been regarded as a treatment of last resort for infections caused by multidrug-resistant *S. aureus.*

C. Antibiotics inhibit protein biosynthesis

As with all living organisms, bacteria possess DNA that encodes the genetic instructions required for the synthesis of proteins essential for survival, including those involved in metabolism, cellular maintenance, growth, and reproduction. Bacterial DNA also specifies the production of three major types of RNA—messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA)—which collectively play central roles in protein biosynthesis. The process of protein synthesis in bacteria occurs through four sequential stages: initiation, elongation, termination, and ribosome recycling. Numerous antibiotics exert their antimicrobial effects by disrupting protein production through interactions with bacterial ribosomes or other components of the translational machinery. These agents selectively target bacterial ribosomes over their eukaryotic counterparts, resulting in a relatively high therapeutic index, although this selectivity is generally lower than that observed for antibiotics that inhibit cell wall synthesis. Drugs within this category can interfere with multiple stages of the protein synthesis pathway.

The Aminoglycoside Drugs

Aminoglycosides are antibiotics composed of one or more amino sugars linked to a six-carbon aminocyclitol ring. These structurally complex compounds are primarily produced by soil-dwelling Actinomycetes, particularly species in the genera *Streptomyces* and *Micromonospora*. For example, streptomycin, kanamycin, neomycin, and tobramycin are synthesized by different *Streptomyces* species, whereas gentamicin is obtained from *Micromonospora purpurea*. While the clinical use of streptomycin has declined due to widespread resistance, it remains an option in specific cases where other aminoglycosides may be unsuitable, such as potential drug interactions. Gentamicin is commonly employed to treat infections caused by Gram-negative bacteria, including *Proteus*, *Escherichia*, *Klebsiella*, and *Serratia*. However, aminoglycosides are associated with significant toxicity, potentially causing nephrotoxicity, ototoxicity, vestibular dysfunction, nausea, and allergic reactions.

The mechanism of action of aminoglycosides involves binding to the 30S subunit of the bacterial ribosome, thereby disrupting protein synthesis. These antibiotics are bactericidal, particularly against Gram-negative pathogens. Binding of aminoglycosides to the ribosome leads to the incorporation of incorrect amino acids into newly synthesized proteins. Misfolded proteins destined for secretion are inserted into the bacterial plasma membrane, which perturbs cellular metabolic pathways and triggers the formation of reactive oxygen species, such as hydroxyl radicals. This dual effect—interference with protein synthesis and increased oxidative stress—explains the bactericidal rather than bacteriostatic nature of aminoglycosides.

Tetracyclines Antibiotics

Tetracyclines are a class of antibiotics characterized by a core four-ring structure to which different side chains are attached. In 1948, a soil-derived Streptomyces strain produced a compound called

aureomycin, which exhibited strong antimicrobial activity and served as the basis for synthesizing related antibiotics, including terramycin and tetracycline. Naturally occurring tetracyclines, such as chlortetracycline and oxytetracycline, are directly produced by Streptomyces species, while others are semisynthetic derivatives. Like aminoglycosides, tetracyclines target the bacterial 30S ribosomal subunit, thereby interfering with protein synthesis. However, unlike aminoglycosides, their effect is bacteriostatic rather than bactericidal. Tetracyclines are broad-spectrum agents, effective against a wide range of bacteria, including intracellular pathogens such as Rickettsia, Chlamydia, and Mycoplasma species.

Macrolide antibiotics

Macrolide antibiotics are characterized by a lactone ring composed of 12 to 22 carbon atoms, which is typically attached to one or more sugar moieties. These antibiotics are naturally produced by the soil bacterium *Saccharopolyspora erythraea* (formerly known as *Streptomyces erythreus*). Macrolides inhibit bacterial protein synthesis by reversibly binding to the P site of the 50S (large) ribosomal subunit. They are most effective against Gram-positive cocci and certain intracellular pathogens, including *Mycoplasma*, *Chlamydia*, and *Legionella* species. Erythromycin was the first macrolide to be discovered, and subsequent derivatives include azithromycin, clarithromycin, and roxithromycin. While their primary effect is bacteriostatic, macrolides can exhibit bactericidal activity at higher concentrations or depending on the susceptibility of the target microorganism.

Chloramphenicol

Chloramphenicol, first isolated in the late 1940s from *Streptomyces venezuelae*, is a powerful broad-spectrum antibiotic distinguished by its nitrobenzene chemical structure. Its primary mechanism of action is the inhibition of protein synthesis through the prevention of peptide bond formation. Unlike its original naturally derived form, chloramphenicol is now produced entirely by chemical synthesis. While it exhibits a spectrum of activity comparable to that of tetracyclines, its clinical use is limited due to significant toxicity to human cells.

D. Folic acid metabolism inhibitors

Sulfonamides, commonly referred to as sulfa drugs, are chemically related to sulfanilamide, which is an analogue of p-aminobenzoic acid (PABA). PABA serves as a key cofactor for several enzymes and is essential for the synthesis of folic acid. Folic acid, in turn, is a precursor for purine and pyrimidine nucleotides, which are required for the synthesis of DNA, RNA, and other critical cellular molecules such as ATP. When a sulfonamide enters a bacterial cell, it competes with PABA for the active site of enzymes involved in folate biosynthesis, leading to reduced folate availability. This disruption inhibits the production of purines and pyrimidines, thereby halting DNA replication and protein synthesis. Sulfonamides generally have a high therapeutic index, but their clinical effectiveness has been limited by the rise of resistant bacterial strains. Trimethoprim, a synthetic antimicrobial, also targets folic acid biosynthesis, further interfering with nucleotide production.

Application of Antibiotics

Antibiotics are employed across multiple sectors, including human medicine, agriculture, aquaculture, and livestock production (Table 1). They are primarily used to treat bacterial infections in humans, animals, and crops, helping to prevent losses due to bacterial diseases. In animal husbandry, antibiotics are also widely applied as growth-promoting agents. The use of antibiotics in livestock is generally categorized into three groups: therapeutic, prophylactic, and growth-promoting applications. Therapeutic antibiotics are administered at high doses to treat clinically ill animals, whereas prophylactic antibiotics are given at sub-therapeutic levels through feed or drinking water to prevent disease in animals that do not show signs of infection. These agents are often administered at intervals throughout the animal's life cycle. Growth-promoting antibiotics, on the other hand, are incorporated into feed in small amounts to enhance growth rates and production efficiency. In aquaculture, antibiotics are used to manage bacterial infections in fish, typically by inclusion in specialized feed formulations. A significant portion of these drugs—approximately 75%—is excreted into the aquatic environment, contributing to environmental exposure.

Table 1 Use of Antibiotics in different sectors

Sectors	Use of Antibiotics

Animal husbandry	Treatment of bacterial infections, Growth promoting agents
Agricultural activities	Prevention of crop loss from bacterial diseases
Aquaculture	Treatment of fish diseases
Human health	Treatment of bacterial infections

Alternative Approaches to Combat Antibiotic Resistance

To address the growing problem of antibiotic resistance, several alternative strategies are being explored. These include bacteriophage therapy, probiotics, nanoparticles (NPs), antimicrobial plant-derived compounds, RNA-based treatments, aptamers, peptide-based therapies, and immunotherapeutic approaches. Some of the key alternative strategies are summarized as follows:

Botanicals

Botanicals, which include whole plants or specific plant parts, produce a variety of secondary metabolites such as alkaloids, flavonoids, phenolics, quinones, tannins, coumarins, terpenes, lectins, and saponins. Many of these compounds, including alkaloids, tannins, and polyphenols, have demonstrated potential as antimicrobial agents and modulators of resistance. Plant-derived extracts can interact with protein domains, leading to the modification or inhibition of protein–protein interactions. This ability allows botanicals to act as modulators of host cellular processes, including immune responses, mitosis, apoptosis, and signal transduction. Consequently, their antimicrobial effects may arise not only from directly inhibiting or killing microorganisms but also by interfering with critical steps in the pathogenic process, reducing the likelihood that bacteria, fungi, or viruses develop resistance to these plant-based compounds.

Bacteriophages

Bacteriophages, as highlighted by the National Institutes of Health (NIH, 2014), represent a promising strategy to counteract microbial resistance. Phage therapy provides a potential alternative to traditional antibiotics for the treatment of bacterial infections. In several Eastern European countries, including Russia and Georgia, phage cocktails are commercially available, and their formulations are regularly updated to include phages effective against newly emerging pathogenic strains. Both human and animal studies have demonstrated that bacteriophages can successfully treat infections caused by a range of bacterial pathogens, such as *Shigella dysenteriae*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Clostridioides difficile*, vancomycin-resistant *Enterococcus faecium*, β-lactamase-producing *Escherichia coli*, imipenem-resistant *P. aeruginosa*, *Acinetobacter baumannii*, and other *E. coli* strains. In practice, phages are administered orally, applied topically to infected wounds or contaminated surfaces, or used during surgical procedures. Intravenous injection is uncommon, both to minimize the risk of introducing residual bacterial contaminants from phage production and because the immune system can rapidly neutralize viruses circulating in the bloodstream or lymphatic system.

Antibiotic Adjuvants

Antibiotic adjuvants (AAs) are compounds that work in combination with antibiotics to increase bacterial susceptibility and enhance the effectiveness of treatment. In addition to boosting antimicrobial activity, they can also influence the host's immune response. A well-known example is beta-lactamase inhibitors, small molecules that, when paired with beta-lactam antibiotics, have been successfully used for over three decades to treat both Gram-positive and Gram-negative infections, with extensive clinical documentation.

Antibiotic adjuvants have gained attention as a promising strategy to combat multi-drug-resistant bacteria and restore the potency of existing antibiotics. These adjuvants may act by directly interfering with bacterial resistance mechanisms or by amplifying the activity of the antibiotic. Compared to developing entirely new antibiotics, the use of adjuvants offers several advantages. They can reduce the minimum inhibitory concentration required for bacterial killing, thereby enhancing the efficacy of currently available drugs. Furthermore, reintroducing previously ineffective antibacterial compounds as adjuvants opens avenues for designing multiple analogues. The combined use of adjuvants and antibiotics can also slow the emergence of resistance by targeting highly conserved bacterial structures, creating a synergistic effect in which the antimicrobial activity of the combination exceeds that of either agent alone.

Nano Antibiotics

Frequent exposure to antibiotics is a major factor driving the development of bacterial resistance. Nanoantibiotics (nAbts) represent a promising application of nanotechnology, where antibiotic molecules—either naturally occurring or synthetically produced—are combined with nanoparticles (NPs) at sizes of ≤100 nm in at least one dimension. This innovative approach enhances the efficacy of existing antibiotics, enabling them to act against clinically significant bacterial strains through nanoscale reengineering. Depending on their design, antibiotic molecules can be incorporated into the core or corona of a nanoconjugate, or they may be attached to nanoparticles without distinct core-corona structures, either chemically or physically.

Nanoparticles used in nAbts can be elemental, such as silicon (Si), iron (Fe), gold (Au), silver (Ag), or titanium (Ti), or they can be functionalized with chemical coatings like carboxylates (-COOH), citrate, polyvinylpyrrolidone (PVP), or various polymers to enhance stability and targeting. These nanoparticles range in size from 1 nm to 100 nm, making them suitable for drug delivery, controlled release, and efficient transport into bacterial cells and human tissues. NPs may be naturally occurring, incidental, or engineered, with engineered NPs being the most widely applied in microbiology. Common types include inorganic and transition metal nanoparticles (e.g., Ag, Au, Pt, Zn, Ti, Al, Fe, Ni, Cu, Si), their oxides (e.g., ZnO, TiO_2, Fe_3O_4, CuO, SiO_2), and carbon-based structures such as liposomes, micelles, dendrimers, fullerenes, carbon nanotubes (CNTs), graphene, and its derivatives.

Antibiotic Inactivation

One of the key mechanisms by which bacteria develop antibiotic resistance is through the inactivation of the drugs. In this process, bacteria produce specific enzymes that chemically alter or degrade the antibiotic, rendering it ineffective. The primary types of these inactivating enzymes include β-lactamases, which target β-lactam antibiotics; aminoglycoside-modifying enzymes, which alter aminoglycosides; and chloramphenicol acetyltransferases, which inactivate chloramphenicol.

Chloramphenicol Acetyltransferases:

Chloramphenicol acetyltransferase is an enzyme produced by bacteria that confers resistance to chloramphenicol by inactivating the drug. It catalyzes the transfer of an acetyl group from acetyl-CoA to chloramphenicol, which prevents the antibiotic from binding to bacterial ribosomes and inhibiting protein synthesis. A histidine residue located in the enzyme's C-terminal region is critical for its catalytic activity.

Beta-lactamases:

Beta-lactamases are a major mechanism of antibiotic resistance in Gram-negative bacteria. These enzymes inactivate beta-lactam antibiotics—including penicillins, cephalosporins, cephamycins, monobactams, and carbapenems—by hydrolyzing the beta-lactam ring, although carbapenems are relatively more resistant to hydrolysis. Beta-lactamases were first identified in *Escherichia coli* shortly after penicillin began to be used clinically in the 1940s. The genes encoding these enzymes can be located on the bacterial chromosome, but they are more commonly carried on plasmids or transposons. To date, over 300 beta-lactamases have been described, and they are classified based on their structure following Ambler's scheme into four groups (A–D). Classes A, C, and D contain a serine residue at their active site, whereas class B, the metallo–beta-lactamases, require zinc ions (Zn^{2+}) for activity. Although β-lactamases are predominantly found in Gram-negative bacteria, they have also been observed in *Staphylococcus aureus*. Notably, *S. aureus* possessed beta-lactamase even before penicillin was widely used, but the prevalence of beta-lactamase–producing strains increased rapidly after penicillin became a common therapeutic agent.

Aminoglycoside-modifying enzymes:

Aminoglycoside-modifying enzymes (AMEs) are bacterial proteins that confer resistance to aminoglycoside antibiotics, such as amikacin and gentamicin, by chemically modifying specific hydroxyl (-OH) or amino ($-NH_2$) groups on the drug. These modifications—through phosphorylation, acetylation, or adenylation—prevent the antibiotic from binding to its target on the bacterial 30S ribosomal subunit, rendering it ineffective. AMEs are classified into three main types: acetyltransferases, nucleotidyltransferases, and phosphotransferases. Clinically, they pose a significant challenge because their genes are frequently located on mobile genetic elements, such as plasmids and transposons, which facilitates rapid dissemination among bacterial populations. These enzymes have been identified in pathogenic strains of *Staphylococcus aureus*, *Enterococcus faecalis*, and *Streptococcus pneumoniae*.

CONCLUSION

This review has explored multiple facets of antibiotics, including their modes of action, the growing challenge of antibiotic resistance, and potential strategies to overcome this issue. While antibiotics are widely used across medical, agricultural, and industrial sectors, their effectiveness is increasingly compromised by the emergence of resistant bacterial strains. Antibiotics function primarily through four mechanisms to inhibit or kill bacteria, yet bacteria have evolved diverse strategies to evade these effects. In light of the limitations of conventional antibiotics, several promising alternative approaches have been highlighted, including the development of new antibiotics, the use of antibiotic adjuvants, nanoparticle-based antibiotics, plant-derived compounds, and bacteriophage therapy. Although the discovery of entirely new antibiotics is difficult, integrating complementary strategies such as nanoantibiotics, adjuvants, botanicals, and phage-based treatments offers a multifaceted approach to mitigating the global antibiotic resistance crisis.

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