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Review Article

Mechanisms of Action and Antimicrobial Resistance: A Comprehensive Review of Antibacterials and Antifungals and Microbial Evolution

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Abstract

The emergence and evolution of antimicrobial agents have revolutionized modern medicine, enabling the effective treatment of bacterial and fungal infections. This article reviews the main mechanisms of action of antibacterial and antifungal agents, including inhibition of cell wall synthesis, protein synthesis, plasma membrane damage, and inhibition of nucleic acids and essential metabolites. The various mechanisms of microbial resistance are also discussed, such as the production of inactivating enzymes, changes in membrane permeability, modification of target sites, efflux systems, and biofilm formation. Microbial evolution through mutations and horizontal and vertical gene transfer is also addressed, highlighting natural selection as a driver of resistance. The conclusion is that the indiscriminate use of antimicrobials has accelerated the emergence of resistant strains, urgently requiring new therapeutic strategies and greater awareness of the rational use of these drugs.

Keywords: *Antibacterials, Antifungals, Mechanisms of Action, Antimicrobial Resistance, Bacterial Evolution, Horizontal Gene Transfer, Selective Toxicity, Biofilms*

1. Introduction

The emergence of modern chemotherapy is credited to the efforts of Paul Ehrlich in Germany during the early twentieth century. While attempting to stain bacteria without staining the surrounding tissues, he speculated about a “magic bullet” that could selectively locate and destroy pathogens without harming the host. This idea laid the foundation for the concept of selective toxicity and for chemotherapy, a term that Ehrlich himself coined. [1,2]

The discovery of antibiotics dates back to the early twentieth century, more specifically to 1928, when the physician and scientist Alexander Fleming accidentally discovered that cultures of the fungus *Penicillium notatum* inhibited the growth of pathogenic bacteria that he had cultivated in the laboratory, particularly *Staphylococcus aureus*. [3] The active compound produced by the mold was subsequently isolated and named penicillin, becoming the first antibiotic ever discovered. It is important to note that the term “antibiotic” refers to a substance produced by microorganisms that, in small quantities, inhibits the growth of another microorganism. Thus, fully synthetic sulfonamide drugs, for example, are technically classified as antimicrobial agents rather than antibiotics. [4]

The discovery of sulfonamides began in 1927 as the result of a systematic search for chemical compounds conducted by German industrial scientists. In 1932, it was found that a compound known as Prontosil Red, a dye containing sulfanilamide, was effective in controlling streptococcal infections in mice [5]. During World War II, this sulfanilamide compound was widely used by Allied armies. The discovery and use of sulfonamides demonstrated that practical antimicrobial agents could effectively combat infectious diseases. As a result, millions of human lives were saved, and life expectancy increased by more than 30 years, particularly in developed countries. [6]

Although antibiotics are now relatively easy to discover, only a few possess significant medical or commercial value. Consequently, there is an increasing urgency to find solutions to the growing problem of antimicrobial resistance, a phenomenon in which previously effective drugs become progressively less effective against pathogenic microorganisms. It is comparatively easy to discover or develop drugs that are effective against bacteria (prokaryotic cells) without affecting human cells (eukaryotic cells). This is because these two cell types differ substantially in several ways, including the presence or absence of a cell wall, the fine structure of their ribosomes, and aspects of their metabolism. Therefore, selective toxicity offers multiple potential targets. The challenge becomes more complex when the pathogen consists of eukaryotic cells, such as fungi, protozoa, or helminths. At the cellular level, these organisms resemble human cells much more closely than bacterial cells do. Consequently, drugs targeting these pathogens often cause damage to the host as well. Our therapeutic arsenal against these types of pathogens is therefore much more limited than our arsenal of antibacterial agents. Viral infections are also particularly difficult to treat because the pathogen resides within the host cell. [7,8]

Some drugs have a narrow spectrum of antimicrobial activity, meaning they affect only a limited range of microbial types. Penicillin G, for example, is active against Gram-positive bacteria but only a few Gram-negative bacteria. Antibiotics that affect a wide variety of Gram-positive and Gram-negative bacteria are known as broad-spectrum antibiotics. [9]Since the identity of a pathogen is not always immediately recognized, a broad-spectrum drug may appear advantageous because it saves valuable time in initiating treatment. However, the disadvantage is that these drugs also destroy a large portion of the host’s normal microbiota. The normal microbiota generally competes with and restricts the growth of pathogens and other microorganisms. If an antibiotic is unable to eliminate certain organisms within the normal microbiota while eliminating their competitors, the surviving organisms may proliferate and become opportunistic pathogens. A commonly observed example is the overgrowth of the yeast *Candida albicans*, which is not susceptible to antibacterial antibiotics. [10]

Antimicrobial drugs may be classified as bactericidal/fungicidal, meaning that they directly kill microorganisms, or bacteriostatic/fungistatic, meaning that they inhibit microbial growth. In cases of bacteriostasis or fungistasis, the host’s own defense mechanisms, such as phagocytosis and antibody production, are generally responsible for eliminating the microorganism. [11]

2. Mechanisms of Action of Antibacterial Agents

2.1 Inhibition of Cell Wall Synthesis

Among the mechanisms of action specifically employed by antibacterial agents are inhibition of cell wall synthesis, inhibition of protein synthesis, damage to the plasma membrane, inhibition of nucleic acid synthesis, and inhibition of the synthesis of essential metabolites. [12]

The first mechanism consists of inhibiting bacterial cell wall synthesis. The bacterial cell wall is composed of a macromolecular network called peptidoglycan. This structure is a repeating disaccharide linked by polypeptides to form a mesh-like network that surrounds the entire cell. The disaccharide portion is composed of the monosaccharides N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM).

These molecules alternate and are linked into chains of 10 to 65 sugar units, forming a carbohydrate "backbone." Penicillin and several other antibiotics interfere with the final cross-linking of peptidoglycan strands, thereby preventing the synthesis of intact peptidoglycan. As a consequence, the cell wall becomes weakened, leading to cell lysis. Since penicillin acts on the process of cell wall synthesis, only actively growing cells are affected by these antibiotics. Furthermore, because human cells do not possess peptidoglycan-containing cell walls, penicillin exhibits low toxicity toward host cells. Cell wall synthesis inhibitors include natural penicillins, semisynthetic penicillins, cephalosporins, polypeptide antibiotics, and antimycobacterial agents. [13]

The first group, the penicillins, comprises more than 50 chemically related antibiotics. All penicillins share a common core structure containing a β-lactam ring, known as the nucleus. Different types of penicillin are distinguished by the chemical side chains attached to this nucleus. Penicillins prevent cross-linking between peptidoglycan molecules, thereby interfering with the final stages of cell wall construction, particularly in Gram-positive bacteria. Penicillins may be produced naturally or semisynthetically. Among the natural penicillins is penicillin G, which has a relatively narrow but useful spectrum of activity and is often the drug of choice against most staphylococci, streptococci, and several spirochetes. [14]

Natural penicillins have some disadvantages. The most important are their narrow spectrum of activity and their susceptibility to penicillinases. Penicillinases are enzymes produced by many bacteria, especially species of Staphylococcus, that cleave the β-lactam ring of the penicillin molecule. Because of this characteristic, penicillinases are often referred to as β-lactamases. To overcome the limitations of natural penicillins, a variety of semisynthetic penicillins have been developed. Scientists produce these compounds in two ways. First, they may interrupt the synthesis of the molecule by *Penicillium* species and isolate only the common penicillin nucleus for further modification. Second, they may remove the side chains from complete natural penicillin molecules and chemically add alternative side chains that make the compounds more resistant to penicillinases or broaden their spectrum of activity. Hence the term semisynthetic: part of the penicillin molecule is produced by the mold, while another part is added synthetically. [15,16]

Cephalosporins possess a core structure similar to that of penicillins and therefore inhibit cell wall synthesis through a mechanism essentially similar to that of penicillins. Their use is more widespread than that of any other β-lactam antibiotic. Although the β-lactam ring of cephalosporins differs slightly from that of penicillin, bacteria have evolved β-lactamases capable of inactivating it. Cephalosporins are commonly classified according to their generations, reflecting their continued development over time. [17]

Polypeptide antibiotics also inhibit bacterial cell wall synthesis, with bacitracin and vancomycin being the most common examples. Bacitracin is a polypeptide antibiotic that is particularly effective against Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus*. It inhibits bacterial cell wall synthesis at an earlier stage than penicillins and cephalosporins by interfering with the synthesis of linear peptidoglycan strands. Its use is generally restricted to topical applications for superficial infections. [18]

Vancomycin belongs to a small group of glycopeptide antibiotics derived from a species of *Streptomyces*. Originally, vancomycin toxicity was a serious concern; however, improvements in purification processes during manufacturing have largely resolved this issue. Although its spectrum of activity is relatively narrow and based on inhibition of cell wall synthesis, vancomycin has played a crucial role in combating methicillin-resistant *Staphylococcus aureus* (MRSA). It has long been considered the last line of antibiotic defense for the treatment of *S. aureus* infections resistant to other antibiotics. However, the widespread use of vancomycin in the treatment of MRSA has contributed to the emergence of vancomycin-resistant enterococci. [19]

The cell wall of members of the genus *Mycobacterium* differs from that of most other bacteria. It contains mycolic acids, which are responsible for its distinctive staining properties and acid-fast nature. This genus includes important pathogens, such as those responsible for tuberculosis and leprosy. Isoniazid (INH) is a synthetic antimicrobial drug that is highly effective against *Mycobacterium tuberculosis*. Its primary effect is the inhibition of mycolic acid synthesis, a cell wall component found exclusively in mycobacteria. Consequently, it has little effect on bacteria belonging to other genera. [20,21]

2.2 Inhibition of Protein Synthesis

In the second mechanism, antibacterial agents act by inhibiting protein synthesis. Although this process is common to all cells, whether prokaryotic or eukaryotic, it would appear to be an unlikely target for selective toxicity. However, a notable difference between prokaryotes and eukaryotes lies in the structure of their ribosomes.

Eukaryotic cells possess 80S ribosomes, whereas prokaryotic cells contain 70S ribosomes. This structural difference is the basis for the selective toxicity of antibiotics that interfere with protein synthesis. Nevertheless, mitochondria, which are important eukaryotic organelles, also contain 70S ribosomes similar to those found in bacteria. Consequently, antibiotics that affect 70S ribosomes may produce adverse effects in host cells. The principal antibiotics that interfere with protein synthesis include chloramphenicol, aminoglycosides, tetracyclines, glycylcyclines, and macrolides. [22]

Chloramphenicol inhibits peptide bond formation in nascent polypeptide chains by interacting with the 50S subunit of the prokaryotic 70S ribosome. Because its structure is relatively simple, it is more economical for the pharmaceutical industry to synthesize it chemically than to isolate it from *Streptomyces*. This antibiotic is relatively inexpensive and has a broad spectrum of activity, making it widely used in settings where low cost is essential. Its small molecular size allows diffusion into areas of the body that are inaccessible to many other drugs. However, chloramphenicol is associated with serious adverse effects, including suppression of bone marrow activity, which impairs blood cell production. Physicians are therefore advised not to use the drug for trivial infections or when suitable alternatives are available. Other antibiotics that inhibit protein synthesis by binding to the same ribosomal site targeted by chloramphenicol include clindamycin and metronidazole. [23]

Aminoglycosides constitute a group of antibiotics in which amino sugars are linked by glycosidic bonds. These antibiotics interfere with the early stages of protein synthesis by altering the conformation of the 30S subunit of the prokaryotic 70S ribosome. This interference results in the misreading of the genetic code carried by mRNA. Aminoglycosides were among the first antibiotics to demonstrate significant activity against Gram-negative bacteria. The best-known aminoglycoside is probably streptomycin, discovered in 1944. Streptomycin is still used as an alternative drug for the treatment of tuberculosis; however, the rapid development of resistance and its serious toxic effects have reduced its clinical utility. Aminoglycosides may impair hearing by causing permanent damage to the auditory nerve, and nephrotoxicity has also been reported. Consequently, their use has declined. Another member of this group, gentamicin, is particularly useful in the treatment of *Pseudomonas* infections, which represent a major problem in individuals with cystic fibrosis. [24,25]

Tetracyclines constitute a closely related group of broad-spectrum antibiotics produced by species of *Streptomyces*. These antibiotics interfere with the binding of amino acid-carrying tRNA molecules to the 30S subunit of the prokaryotic 70S ribosome, thereby preventing the addition of amino acids to growing polypeptide chains. They do not interfere with mammalian ribosomes because they do not efficiently penetrate intact eukaryotic cells. However, small amounts of the drug may enter host cells, which explains why intracellular pathogens such as chlamydiae and rickettsiae are susceptible to tetracyclines. In these cases, the selective toxicity of the drug results from the greater sensitivity of bacterial ribosomes. In addition to being effective against both Gram-positive and Gram-negative bacteria, tetracyclines readily penetrate body tissues and are especially valuable in the treatment of infections caused by intracellular chlamydiae and rickettsiae. Three of the most commonly used tetracyclines are oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and tetracycline itself. [26]

Tetracyclines are used in the treatment of many urinary tract infections, mycoplasma pneumonia, and infections caused by chlamydiae and rickettsiae. They are also frequently employed as alternative drugs in the treatment of diseases such as gonorrhea and syphilis. Due to their broad spectrum of activity, tetracyclines often suppress the normal intestinal microbiota, causing gastrointestinal discomfort and frequently leading to superinfections, particularly those caused by the fungus *Candida albicans*. These drugs are not recommended for use in children, in whom they may cause brown discoloration of the teeth, or in pregnant women, who may experience liver damage. [27]

Glycylcyclines are a relatively new class of antibiotics that emerged after the year 2000. They are structurally similar to tetracyclines. The best-known example is tigecycline (Tygacil). This broad-spectrum bacteriostatic antibiotic binds to the 30S ribosomal subunit, thereby blocking protein synthesis. A major advantage of glycylcyclines is their ability to overcome rapid efflux mechanisms, which constitute an important form of bacterial resistance to antibiotics. Among their disadvantages is the requirement for slow intravenous infusion. This class of antibiotics is particularly useful against MRSA and multidrug-resistant strains of Acinetobacter baumannii. [28–30]

Macrolides constitute a group of antibiotics named after the presence of a macrocyclic lactone ring. The best-known macrolide used in clinical practice is erythromycin. Its mechanism of action involves inhibition of protein synthesis, apparently through blockage of the ribosomal exit tunnel. However, erythromycin is unable to penetrate the cell wall of most Gram-negative bacilli.

Erythromycin is the drug of choice for the treatment of legionellosis, mycoplasma pneumonia, and several other infections. Other macrolides that have become available more recently include azithromycin and clarithromycin. Compared with erythromycin, these agents possess a broader antimicrobial spectrum and improved tissue penetration. This characteristic is particularly important in the treatment of infections caused by intracellular bacteria such as chlamydiae. [31,32]

In addition to these groups, other antibiotics also act by inhibiting protein synthesis, including streptogramins, oxazolidinones, and pleuromutilins. These agents have been developed over the years in response to the increasing problem of bacterial resistance to antibiotics and synthetic antimicrobial drugs discovered to date. [33–35]

2.3 Damage to the Plasma Membrane

In addition to targeting proteins, antimicrobial drugs may act by causing damage to the plasma membrane, as is the case with certain polypeptide compounds. These agents alter membrane permeability, resulting in the loss of essential metabolites from the microbial cell. The synthesis of the bacterial plasma membrane requires the production of specific fatty acids, which serve as structural building blocks. In the search for attractive targets for new antibiotics, researchers have focused on this metabolic pathway because it differs significantly from fatty acid biosynthesis in humans. Interference with this process forms the basis of the mechanism of action of several antibiotics and antimicrobial agents. One limitation of this approach, however, is that many bacterial pathogens are capable of acquiring fatty acids directly from serum. Examples of drugs that act through this mechanism include lipopeptide antibiotics. [36]

Among these agents, daptomycin (Cubicin), produced by a species of *Streptomyces*, is an antibiotic effective exclusively against Gram-positive bacteria. Its use has been approved for certain skin and soft tissue infections. Its apparent mechanism of action involves disruption of the bacterial cell membrane, and resistance to this drug remains uncommon. Because of its unique mode of action, daptomycin is often employed in the treatment of infections caused by multidrug-resistant bacteria. [37] Polymyxin B, in contrast, is a bactericidal antibiotic that is highly effective against Gram-negative bacteria. For many years, it was one of the few drugs available for the treatment of infections caused by bacteria of the genus *Pseudomonas*. Today, its use is relatively uncommon, except in the topical treatment of superficial infections, for which polymyxin B remains available in antiseptic ointments. [38]

2.4 Inhibition of Nucleic Acid Synthesis

Several antibiotics interfere with the processes of DNA replication and transcription in microorganisms. Some drugs with this activity have extremely limited clinical utility because they also interfere with mammalian DNA and RNA metabolism. As a result, they exhibit low selectivity and high toxicity. Among these agents are the rifamycins, quinolones, and fluoroquinolones. The best-known derivative of the rifamycin family of antibiotics is rifampicin (rifampin). These drugs are structurally related to macrolides and inhibit the synthesis of mRNA. Undoubtedly, the most important use of rifampicin is against mycobacteria, particularly in the treatment of tuberculosis and leprosy. A valuable characteristic of this drug is its ability to penetrate tissues and achieve therapeutic concentrations in cerebrospinal fluid and abscesses. This property is likely an important factor in its antitubercular activity, since the pathogen responsible for tuberculosis is often located within tissues or macrophages. A distinctive side effect of rifampicin is the red-orange discoloration of urine, feces, sweat, saliva, and even tears. [39,40]

Quinolones were developed during the 1960s, with nalidixic acid being the first synthetic drug of this class. It became known for its unique bactericidal effect, achieved through the selective inhibition of DNA gyrase, an enzyme required for DNA replication. Although the clinical use of nalidixic acid was limited, primarily to the treatment of urinary tract infections, it led to the development in the 1980s of a prolific group of synthetic quinolones known as fluoroquinolones. This group is divided into two subgroups, each displaying a progressively broader spectrum of activity. Early-generation fluoroquinolones include norfloxacin and ciprofloxacin, both of which are widely used. Ciprofloxacin is particularly well known by its trade name, Cipro, and for its use in the treatment of anthrax infections. A more recent group of fluoroquinolones includes gemifloxacin and moxifloxacin. These antibiotics, with the exception of moxifloxacin, are frequently the drugs of choice for the treatment of urinary tract infections and certain types of pneumonia. As a class, fluoroquinolones are relatively non-toxic. However, resistance to these agents may develop rapidly, even during the course of treatment. [41]

2.5 Inhibition of Essential Metabolite Synthesis

Finally, antibacterial agents may act by inhibiting the production of metabolites that are essential for bacterial cell survival. This occurs when the enzymatic activity of a microorganism is competitively inhibited by a substance known as an antimetabolite, which closely resembles the enzyme's normal substrate. Sulfonamides, or sulfa drugs, were among the first antimicrobial therapies to be developed. Folic acid is an important coenzyme required for the synthesis of proteins, DNA, and RNA. Sulfonamides are structurally similar to para-aminobenzoic acid (PABA), a precursor of folic acid. This similarity allows them to competitively bind to the enzyme that normally utilizes PABA, thereby blocking the production of folic acid. Folic acid functions as a coenzyme in the synthesis of purine and pyrimidine bases of nucleic acids, as well as many amino acids. Sulfonamides are bacteriostatic agents and do not damage human cells because humans do not synthesize folic acid; instead, it is obtained through the diet. Consequently, the selective toxicity of sulfonamides is based on the fact that bacteria must synthesize their own folic acid, whereas human cells rely on an external dietary source. [42,43]

3. Mechanisms of Action of Antifungal Agents

As previously mentioned, eukaryotic organisms such as fungi utilize the same mechanisms of protein and nucleic acid synthesis as higher animals, including humans. Consequently, it is much more difficult to identify targets that ensure selective toxicity in eukaryotes than in prokaryotes. For this reason, antifungal agents emerged considerably later than antibacterial agents. Early antifungal therapy was largely ineffective and nonspecific, with potassium iodide being the first compound used, in 1903. Since then, the search for more effective and less toxic antifungal drugs has intensified. In this context, griseofulvin was discovered in 1939, although its clinical use for the treatment of dermatophytic infections only began in 1958. The development of antifungal drugs remains particularly important because fungal infections have become increasingly common as opportunistic infections in immunocompromised individuals, especially those with AIDS. [44]

Given these challenges, it is evident that antifungal mechanisms of action are more limited than those available for antibacterial agents. The major mechanisms include agents that affect fungal sterols, agents that affect the fungal cell wall, and nucleic acid synthesis inhibitors. In the first mechanism, many antifungal drugs target sterols present in the plasma membrane. In fungal membranes, the principal sterol is ergosterol, whereas in higher animals the predominant sterol is cholesterol. When ergosterol synthesis is blocked, the fungal membrane becomes excessively permeable, ultimately leading to cell death. Thus, inhibition of ergosterol biosynthesis forms the basis of the selective toxicity of many antifungal drugs, including members of the polyene, azole, and allylamine groups. [45,46]

Polyene derivatives such as amphotericin B and nystatin are examples of antibiotics with antifungal activity whose primary action is to alter fungal membrane permeability. Among the antifungal drugs currently available, amphotericin B is one of the most difficult to administer and is associated with numerous adverse effects. However, during the 1990s, three lipid formulations were introduced, the best known being liposomal amphotericin B, which exhibits improved tolerability. This drug may be administered alone or in combination with other antifungal agents, since pharmacological synergism allows lower doses of amphotericin B to be used, thereby reducing adverse effects. Nystatin, another polyene macrolide, has a molecular structure and pharmacodynamic profile similar to amphotericin B and is active against yeasts of the genus Candida. It is primarily available as topical ointments and vaginal creams. [47–50]

These polyene derivatives bind to ergosterol within the fungal cell membrane, forming pores and channels that increase membrane permeability. As a result, there is a substantial loss of intracellular molecules and electrolytes, particularly potassium, disrupting cellular homeostasis and leading to fungal cell death. Amphotericin B is distributed throughout the body, including the placenta. However, it penetrates poorly into certain body fluids, such as cerebrospinal fluid, vitreous humor, and synovial fluid. [48,51]

The azoles constitute a group of synthetic compounds with similar chemical structures and a broad spectrum of antifungal activity. Many are also effective against certain Gram-positive bacteria. The investigation of antifungal activity within this class began with benzimidazole, leading to the development of imidazole and triazole derivatives, which have become highly important in medical mycology. Their mechanism of action involves interference with ergosterol synthesis through inhibition of the enzyme 14-α-demethylase, a cytochrome P450-dependent enzyme in fungal cells. This inhibition prevents the conversion of lanosterol into ergosterol, resulting in ergosterol depletion.

Consequently, membranes with altered structure and function are formed, while sterol precursors accumulate, particularly 14α-methylfecosterol and 14α-methyl-ergosta-8,24(28)-dien-3β,6α-diol. These changes disrupt membrane function and increase membrane permeability. In addition, azoles may inhibit Erg11 (Cyp51), another key enzyme involved in sterol biosynthesis. [52–54]

Allylamines represent a class of antifungal agents that inhibit ergosterol biosynthesis through a functionally distinct mechanism. Terbinafine and naftifine, examples of this group, are often used when resistance to azole antifungals develops. Depending on the fungal species involved, these drugs may exert either fungicidal or fungistatic activity. Their mechanism is based on inhibition of the enzyme squalene epoxidase, thereby blocking an early step in ergosterol biosynthesis. This inhibition also results in the toxic accumulation of squalene within the fungal cell, ultimately causing cell death. This mechanism is highly specific, as it does not interfere with other enzymes involved in ergosterol synthesis. [55]

The second major mechanism involves antifungal agents that target the fungal cell wall. Fungal cell walls contain compounds unique to these organisms. In addition to ergosterol, β-glucan represents a major target for selective toxicity. A relatively new class of antifungal drugs, the echinocandins, inhibits glucan biosynthesis, resulting in incomplete cell wall formation and subsequent cell lysis. One member of this group, caspofungin (Cancidas), has become particularly valuable in the treatment of systemic *Aspergillus* infections in immunocompromised patients. Echinocandins are also effective against other important fungal infections, including those caused by *Candida* species. [56,57]

Finally, antifungal agents may inhibit nucleic acid synthesis. An example is flucytosine, a pyrimidine analog of cytosine that interferes with RNA biosynthesis and, consequently, protein synthesis. Its selective toxicity is based on the ability of fungal cells to convert flucytosine into 5-fluorouracil, which becomes incorporated into RNA molecules and ultimately blocks protein synthesis. Mammalian cells lack the enzyme required for this conversion. Flucytosine has a relatively narrow spectrum of activity, and its nephrotoxicity and bone marrow toxicity further limit its clinical use. [58]

Other antifungal drugs act through different mechanisms. One example is griseofulvin, an antibiotic produced by a species of *Penicillium*. This drug is particularly effective against superficial dermatophytic infections of the hair and nails. Although administered orally, it selectively binds to keratin in the skin, hair follicles, and nails. Its primary mechanism of action involves inhibition of microtubule synthesis, which interferes with mitosis and thereby inhibits fungal reproduction. For some antifungal agents, however, the precise mechanism of action remains unclear. Examples include tolnaftate, used in the treatment of athlete's foot, and pentamidine, which is used in the treatment of pneumonia. [59,60]

4. Microbial Resistance

The advent of antibiotics marked a major turning point in medicine, as bacterial and fungal infections were responsible for a large number of deaths during the pre-antibiotic era. Antibiotics provided an effective means of overcoming many of these infectious diseases. However, in the mid-twentieth century, when accepting his Nobel Prize, Alexander Fleming warned of the possibility that resistant microorganisms could emerge if antibiotics were used improperly, particularly through inadequate therapy involving low doses or antibiotics of questionable efficacy. Unfortunately, Fleming's prediction proved to be correct. Over the years, the intensive and inappropriate use of antimicrobial agents has selected for resistant microorganisms. These organisms are capable of growing and multiplying in the presence of antibiotic concentrations that would normally inhibit their growth. Although resistance is most commonly associated with bacteria, it also occurs among fungi and protozoa. [61,62]

The consequences of irrational antimicrobial use have led to the emergence of antimicrobial resistance, one of the greatest public health challenges of the modern era. This issue has become so serious that the World Health Organization (WHO) has repeatedly highlighted the urgent need for the development of new strategies to combat antimicrobial resistance. The concern stems from the fact that antimicrobial resistance is among the leading causes of death worldwide, contributing to millions of deaths each year. In addition to its impact on human health, antimicrobial resistance imposes substantial economic burdens on healthcare systems due to increased treatment costs and prolonged hospitalizations. [63]

Despite the development of numerous new antimicrobial agents following the discovery of penicillin, resistance remains a persistent problem. One of the main reasons is the excessive and inappropriate use of these drugs, often as prophylactic measures against potential bacterial infections without proper indication. As a result, projections suggest that by 2050 antimicrobial-resistant infections could be responsible for approximately 10 million deaths annually worldwide. Such a scenario raises concerns that modern healthcare could be pushed toward a “post-antibiotic era,” in which many previously treatable infections once again become life-threatening. [64,65]

5. Evolution and Dissemination of Resistance

The mechanisms of bacterial resistance to chemotherapeutic agents are responsible for bacterial survival and multiplication in the presence of antimicrobial drugs. These mechanisms include enzymatic destruction or inactivation of the drug, alterations in antibiotic uptake, modifications of drug target sites, protection or shielding of target sites, and active antibiotic efflux. Enzymatic destruction or inactivation primarily affects natural antibiotics such as penicillins and cephalosporins and is generally less effective against synthetic antibacterial drugs such as fluoroquinolones, since microorganisms have had less evolutionary time to adapt to these relatively unfamiliar chemical structures. In this mechanism, bacterial cells produce enzymes capable of destroying or inactivating the active compounds of antibiotics. In the case of β-lactam antibiotics, the β-lactam ring is targeted and cleaved by β-lactamase enzymes, thereby inactivating the antibiotic. [66,67]

Gram-negative bacteria are intrinsically less permeable to many antibiotics because their cell wall contains an outer membrane, a structure absent in Gram-positive bacteria. Therefore, reduced outer membrane permeability is a resistance mechanism unique to Gram-negative bacteria. To reach their intracellular targets within the periplasm or cytoplasm, antibiotics must cross the outer membrane or the entire cell wall. Hydrophilic antibiotics, which are generally small molecules, enter through passive diffusion via outer membrane proteins known as porins. Reduced permeability may result from structural alterations in porins or complete loss of porins, leading to increased selectivity or even impermeability to antibacterial drugs. This mechanism mainly affects the entry of β-lactam antibiotics and fluoroquinolones. [68]

Most antibiotics bind specifically to one or more targets within the bacterial cell. Structural alterations in these targets prevent efficient binding or reduce the affinity of the interaction, causing the antibiotic to no longer recognize its target. Such target modifications generally arise from mutations in bacterial genes. These changes interfere with antimicrobial binding while preserving the essential function of the altered target, allowing the bacterium to maintain its physiological activities and evade antibiotic action. One of the best-known examples is chromosomal mutations within quinolone resistance-determining regions (QRDRs).[69,70]

Target protection or shielding may occur through the production of enzymes or cellular structures that prevent antibiotic binding to the target site. An example of target protection is the production of *Qnr* proteins, which bind to and protect DNA topoisomerase II from the action of quinolones, thereby reducing bacterial susceptibility to these antibiotics. An example of target shielding is the thickening of the cell wall in *Staphylococcus aureus*, mediated by the expression of chromosomal genes. This thickened wall acts as a barrier, preventing glycopeptides such as vancomycin and teicoplanin from reaching their target sites, resulting in intermediate resistance to these drugs. [71]

Efflux systems are natural mechanisms used by bacteria to expel toxic substances generated during metabolism. These systems are typically located in the bacterial cell envelope and are generally encoded by chromosomal genes. Clinically significant resistance occurs when these systems become overexpressed, either through increased numbers of efflux pumps or enhanced pump activity. In Gram-negative bacteria, due to the presence of the outer membrane, efflux systems usually consist of an inner membrane transporter (the efflux pump), an outer membrane protein (a porin), and a linking protein connecting the two. In Gram-positive bacteria, which lack an outer membrane, the efflux system consists solely of the efflux pump itself. Efflux systems may have broad specificity, expelling multiple antibiotics from different classes, or may be highly specific for a single antibiotic or class. Plasmid-mediated efflux mechanisms have also been described and often do not depend on overexpression. [72]

As previously discussed, antimicrobial resistance is not restricted to bacteria but also occurs in fungi. Therefore, understanding fungal resistance mechanisms is crucial for interpreting antifungal responses and developing more effective therapeutic strategies. The identification of alternative molecular targets or interference with resistance mechanisms may contribute to combating antifungal-resistant infections.

Resistance mechanisms commonly observed among fungal pathogens can be classified into four categories: (1) transport alterations, (2) target alterations, (3) activation of compensatory pathways, and (4) formation of complex multicellular structures. [73]

Transport alterations leading to antifungal resistance are mediated by various fungal transporters known as efflux pumps. These pumps reduce intracellular drug accumulation by actively expelling antifungal agents before they can reach their intracellular targets. Two major classes of efflux pumps have been identified: ATP-binding cassette (ABC) transporters and major facilitator (MF) transporters. ABC transporters contain four domains: two transmembrane domains and two ATP-binding nucleotide-binding domains (NBDs). An exception is the YEF3 subfamily, whose members lack transmembrane domains. MF transporters have been strongly associated with fluconazole resistance. [74–76]

The second resistance mechanism involves target alteration through mutations and gene upregulation. These target modifications are well-established resistance mechanisms against azoles and echinocandins. Structural changes in the target enzyme prevent effective drug binding. Resistance associated with alterations in Erg11/Cyp51, the target of azoles, has been extensively documented and involves both mutations and overexpression of the corresponding genes. Numerous nonsynonymous nucleotide polymorphisms have been identified in ERG11 alleles from azole-resistant isolates of *Candida albicans*. The high degree of polymorphism observed in ERG11 suggests that Erg11 is highly tolerant of structural changes resulting from amino acid substitutions. [77]

In addition, one of the principal mechanisms through which fungi acquire antifungal resistance involves the activation of compensatory pathways that bypass or neutralize antifungal effects. These pathways may involve alterations in the expression of genes related to antifungal metabolism, drug transport, or target biosynthesis. A notable example is azole resistance mediated by mutations in the ERG3 gene, which encodes the enzyme sterol Δ5,6-desaturase. Erg3 plays a critical role in sterol biosynthesis, including the production of ergosterol, an essential component of fungal cell membranes. In azole-resistant yeast cells, mutations in ERG3 may result in a modified enzyme with reduced or altered activity. Consequently, the conversion of 14α-methylated sterols into toxic 3,6-diol derivatives is altered. This modification in sterol biosynthesis enables fungal cells to survive in the presence of azoles because the resulting metabolites exhibit lower affinity for azole targets or may be removed through efflux mechanisms. This ability to reconfigure metabolic pathways and avoid the accumulation of toxic intermediates represents an important example of evolutionary adaptation. [78–80]

Finally, fungi may exhibit antifungal resistance through the formation of complex multicellular structures such as biofilms. Fungal biofilms are highly organized microbial communities that adhere to and aggregate on surfaces, including inert materials, biological tissues, and medical devices. These three-dimensional structures consist of fungal cells embedded within an extracellular matrix composed of polysaccharides, proteins, and other components produced by the fungi themselves, host cells, or coexisting microorganisms. [81]

Biofilm formation is a dynamic process involving several stages. Initially, fungal cells adhere to a surface through physical and chemical interactions. They subsequently proliferate and produce extracellular matrix material, which surrounds and protects the cells. As the biofilm matures, additional fungal cells adhere and become incorporated into the growing structure, resulting in a complex multicellular community. Fungal cells within biofilms are significantly more resistant to antifungal agents than planktonic cells. The extracellular matrix acts as both a physical and chemical barrier, limiting antifungal penetration. Recent studies suggest that biofilms contain varying proportions of persister cells, phenotypic variants that exhibit enhanced tolerance to antimicrobial agents. Biofilms also contain heterogeneous populations of cells at different growth stages, displaying differential expression of genes associated with drug resistance, such as *ERG11*, *CDR1*, *CDR2*, and *MDR1*. Furthermore, biofilms can sequester antifungal agents, including azoles and amphotericin B, within matrix polymers, thereby reducing their inhibitory effects. [82,83]

These resistance mechanisms arise through microbial evolution, which occurs via random mutations during replication of genetic material, according to neo-Darwinian evolutionary principles. DNA replication is generally highly accurate in both bacteria and fungi, with errors occurring at a rate of approximately one mistake per 10 billion incorporated bases. Much of this fidelity is attributable to proofreading activity by DNA polymerase enzymes. Nevertheless, some replication errors escape correction and become mutations, which may be neutral, harmful, or beneficial. [84]

Neutral mutations, also known as silent mutations, do not alter the activity of the gene product despite changes in the DNA sequence. Such mutations occur when one nucleotide is substituted for another. Even if an amino acid is altered, protein function may remain unchanged if the affected residue is not located within a critical region of the protein or if the replacement amino acid is chemically similar to the original. In contrast, mutations affecting essential regions of proteins may be either detrimental or beneficial. Harmful mutations may render an enzyme inactive or less functional, leading to the loss of an important phenotypic trait. Beneficial mutations, however, may generate new functions or enhance existing ones. It is through such beneficial mutations that microorganisms can acquire resistance to antimicrobial agents. Consequently, the survival and reproduction of organisms carrying advantageous genotypes are favored by environmental conditions, resulting in the selection of specific genes through the process of natural selection. [85,86]

These mutations may subsequently be transmitted both horizontally and vertically among bacteria, whereas vertical transmission is more common in fungi. Horizontal gene transfer occurs when cells exchange genetic material laterally, with one organism donating DNA and another receiving it. This process also occurs in fungi. Horizontal transfer leads to genetic recombination, which refers to the exchange of genetic material between DNA molecules, producing new gene combinations. If a cell acquires exogenous DNA, part of it may integrate into the chromosome through a process known as crossing over. Following incorporation of donor DNA, the remaining genetic material is typically degraded by cellular enzymes. Three principal forms of horizontal gene transfer exist: transformation, conjugation, and transduction. [87,88]During transformation, bacteria or fungi take up free DNA fragments from the environment. These fragments may become incorporated into the genome, conferring new phenotypic traits such as the ability to produce previously absent enzymes. During conjugation, microorganisms acquire new genetic material through plasmid transfer. In bacteria, plasmids are transferred from donor (F+) cells to recipient (F−) cells through sex pili. Because plasmids are extrachromosomal elements, this transfer generally does not harm the donor cell. Conjugation requires direct cell-to-cell contact. [89]

The third mechanism of horizontal gene transfer is transduction, which occurs in bacteria. In this process, bacterial DNA is transferred from a donor cell to a recipient cell by a bacteriophage, a virus that infects bacteria. During phage replication, both phage DNA and proteins are synthesized by the bacterial host cell. As phage DNA is packaged into newly formed viral capsids, bacterial chromosomal or plasmid DNA may occasionally be incorporated instead. This DNA can then be transferred to another bacterium, promoting genetic recombination and potentially conferring new traits such as antibiotic resistance. [90]

Once resistance has been acquired, it can be transmitted through normal reproductive processes, resulting in offspring that inherit the genetic characteristics of their parental microorganisms. This process is known as vertical transmission. Before cell division, the genetic material replicates so that each daughter cell receives a chromosome identical to that of the original cell. DNA replication involves separation of the two strands of the double helix, followed by synthesis of complementary strands using each original strand as a template. In this manner, the genotype is transmitted to subsequent generations. Due to the rapid reproduction rate of bacteria, only a short period of time may be required for an entire bacterial population to become resistant to a newly introduced antibiotic. Microbial evolution can lead to the emergence of new species or strains, adaptation to specific environments, development of antimicrobial resistance, and diversification of biological forms and functions. The study of microbial evolution is therefore essential for understanding microbial biology, ecological interactions, and the development of effective strategies for controlling infectious diseases. [91]

6. Conclusion

In conclusion, advances in antimicrobial chemotherapy have represented a fundamental milestone in medicine, enabling the control of numerous infections that were once potentially fatal. However, the indiscriminate and inappropriate use of these drugs has driven the emergence and spread of antimicrobial resistance, which has become one of the greatest challenges facing public health today. In this context, a thorough understanding of the mechanisms of action of antimicrobial agents, as well as the resistance strategies developed by bacteria and fungi, is essential for the development of new therapeutic approaches. Therefore, the rational use of these agents, combined with continuous investment in research and innovation, is imperative to preserve the effectiveness of existing treatments and to effectively address the growing threat posed by resistant infections.

Conflict of Interest

The authors declare no conflict of interest.

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