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Combatting antimicrobial resistance: Mechanisms, emerging therapies, and future directions

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ABSTRACT

Antimicrobial resistance, or AMR, is one of the major health challenges across the globe because of reduced effectiveness against bacteria, fungi, and viruses. This situation arises when there is significant interference with the effectiveness of antimicrobial agents-antibiotics, antifungals, and antivirals-that are considered essential for treatment. Antimicrobials act selectively against specific targets and metabolic processes of microorganisms. However, pathogens continuously evolve resistance mechanisms and complicate treatment efforts. The modes of action and the mechanisms of resistance are discussed, from the point of view of bacterial, fungal, and viral pathogens, with an overview of emerging therapeutic approaches, such as bacteriophage therapy and plant-derived antimicrobials. Understanding resistance modes is vital to fully harness existing antimicrobials, construct new synthetic agents, and promote responsible antimicrobial stewardship. It will showcase the existing knowledge and identify the gaps in research, therefore providing insight to guide future efforts in addressing AMR.

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Introduction

Antimicrobial resistance (AMR) has risen as one of the global health challenges, suggested to take 10 million lives yearly by 2050 unless something is done about the situation. General misuse and overuse of antibiotics in human medicine, agriculture, and veterinary use are considered the major drivers toward AMR. Drivers are heightened by gaps in the stewardship and regulatory frameworks of antibiotics, especially in low- and middle-income countries. To control this crisis, a unified global effort must monitor antibiotic use, implement regulations, and provide fair healthcare interventions. This will contribute to the far-reaching socioeconomic consequences of AMR and the urgent need for coordinated international actions that seek to reduce its impacts. This will contribute to the far-reaching socioeconomic consequences of AMR

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and the urgent need for coordinated international actions that seek to reduce its impacts (Velazquez-Meza et al., 2022; Tang et al., 2023; Salam et al., 2023).

The mechanisms of developing AMR are varied and differ among the pathogens, usually including genetic mutations, horizontal gene transfer, and phenotypic adaptations. Resistance mechanisms in bacteria include enzymatic degradation of antibiotics, such as β-lactamases, drug target alterations such as mutations in ribosomal RNA genes, and active efflux pumps that expel antibiotics out of cells. Similarly, fungal resistance, such as that observed in *Candida* species, is driven by mutations in ergosterol biosynthesis pathways, while antiviral resistance often involves changes in viral polymerase or protease enzymes (Langford et al., 2023; Tang et al., 2023).

Resistance to antifungal therapies, particularly azoles, is escalating due to environmental exposure and clinical overuse. Multidrug-resistant *Candida auris* represents a major public health concern with limited therapeutic options. In the same way, viruses like human immunodeficiency virus (HIV) and influenza become resistant to antivirals because they change quickly and are under a lot of pressure to stay that way for a long time. However, pathogens such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Acinetobacter baumannii* demonstrate bacterial resistance, which remains the most significant and dangerous issue (Salam et al., 2023; Langford et al., 2023).

The Coronavirus disease 2019 (COVID-19) pandemic has further complicated the challenges of AMR due to increased empirical use of antibiotics, mostly without confirmation of bacterial infection. Multiple drug-resistant organisms, including *Acinetobacter baumannii* and MRSA, are common in intensive care units; secondary bacterial infections are also prevalent. We need to be very cautious when prescribing antibiotics, using rapid diagnostics and local epidemiological data to aid us in doing this to avoid further perpetuating AMR (Langford et al., 2023). Added to that, since the COVID-19 pandemic, there has been a striking increase in the incidence of mucormycosis among those with predisposing factors, especially uncontrolled diabetes and steroid therapy. It is caused by fungal infections from the orders *Mucorales* and *Entomophthorales*. These infections can get into blood vessels and are very dangerous for immunocompromised patients. The most common fungi causing diseases, *Rizopus oryzae*, causes rhinocerebral mucormycosis in humans. In general, the disease usually presents itself as rhinocerebral, pulmonary, cutaneous, or gastrointestinal infections, and has a fast development of the disease shortly after infection begins. Due to the difficulty in diagnosing the disease, it often goes unreported. The most common mode of infection comes through fungal spores that are very common in the soil, plants, and compost. The importance of developing new approaches in fighting against AMR is a necessity (Gupta et al., 2023).

The "One Health" approach underscores the interconnectedness of human, animal, and environmental health in addressing AMR. This strategy advocates for reducing antibiotic misuse in livestock, promoting safe environmental practices, and preventing the spread of resistance genes. Environmental reservoirs, such as water sources contaminated with antibiotic residues, play a significant role in the dissemination of AMR (Velazquez-Meza et al., 2022; Tang et al., 2023).

Antimicrobial stewardship programs (ASPs) are crucial in the fight against AMR because they make the best use of antibiotics to get better clinical outcomes while reducing resistance. These programs emphasize rapid diagnostics to confirm infections, de-escalation of broad-spectrum antibiotics, and adherence to treatment guidelines. Implementing ASPs across hospitals, veterinary practices, and agriculture can significantly reduce unnecessary antibiotic exposure and limit the emergence of resistance. Education and training for healthcare providers are equally critical in fostering prudent antibiotic use (Velazquez-Meza et al., 2022; Tang et al., 2023; Salam et al., 2023). The policies that restrict the non-therapeutic use of antibiotics in agriculture are as important as conducting research to identify alternative therapies. Therefore, the global implementation of ASPs and the establishment of public-private partnerships are crucial in providing funding for research and new drug development (Velazquez-Meza et al., 2022; Salam et al., 2023; Langford et al., 2023). The development of measures to address AMR will depend on a combination of scientific innovation, global cooperation, and broad public health policies. Key strategies include the development of new generations of antimicrobials, clustered regularly interspaced short palindromic repeats (CRISPR)-based therapies, and vaccines against resistant organisms. Improving international surveillance systems and ensuring equitable access to health innovations are indispensable for addressing the gap that exists between rich and poor nations. Moreover, extensive educational initiatives are crucial for enhancing understanding of antibiotic resistance while advocating for the judicious use of antibiotics (Tang et al., 2023; Salam et al., 2023).

This review aims to deliver a comprehensive and detailed discussion on the mechanism of available antimicrobial agents and their emerging resistance mechanisms by microorganisms. It will address emerging antimicrobial therapies, such as bacteriophage therapy and traditional herbal medicine, and their role in combating AMR. Through an integrated analysis of these topics, this

work seeks to advance understanding and inform future efforts in addressing this critical challenge.

Antibacterial Agents and Their Mechanisms of Action

These antibiotics target key microbial targets using diverse approaches to act either as bactericidal or bacteriostatic agents. The major mechanisms of action are discussed below (**Fig. 1**):

1. Interference with Cell Wall Synthesis

The bacterial cell wall composed predominantly of peptidoglycan plays a significant role in maintaining cell shape and preventing lysis. Antibiotics acting on this structure include the β-lactams (penicillins, cephalosporins, carbapenems, and monobactam) and glycopeptides, including vancomycin and teicoplanin. The mechanism of action of β-lactams mimics that of the D-Ala-D-Ala dipeptide, thereby binding to penicillin-binding proteins (PBPs) and subsequently preventing the cross-linking activity of peptidoglycan, compromising the structural integrity of the cell wall (Nikolaidis et al., 2014). Glycopeptides inhibit the cross-linking action between peptidoglycan layers, thus weakening the cell wall and causing cell death, especially in gram-positive bacteria like MRSA and *Enterococcus* species (Cole and Riordan, 2013).

2. Interference with Protein Synthesis

Various drugs interfere with bacterial protein synthesis with minimal interference with human protein synthesis due to differences in ribosomal structure. Antibiotics targeting the 30S ribosomal subunit, such as aminoglycosides and tetracyclines, inhibit translation by causing mistranslation and preventing the correct binding of mRNA to tRNA (Lin et al., 2018). Aminoglycosides act by two mechanisms: they inhibit the initiation complex formation and cause misreading of mRNA, which leads to the incorporation of wrong amino acids and subsequently to the inhibition of protein synthesis. Agents that target the 50S subunit, such as chloramphenicol, bind to the 50S ribosomal subunit and obstruct the peptidyl transferase center and peptide exit tunnel; this interferes with the process of elongation, thereby preventing peptide bond formation (Lin et al., 2018).

3. Inhibition of Nucleic Acid Synthesis

DNA synthesis depends on topoisomerases, particularly DNA gyrase and topoisomerase IV, for the regulation of DNA supercoiling. Fluoroquinolones inhibit these enzymes, thus interfering with DNA replication and inhibiting DNA synthesis within a wide range of bacterial species. Another antimicrobial that acts on nucleic acids is Rifampin. This drug is mainly used in the treatment of tuberculosis in combination with other therapeutic agents. Rifampin inhibits bacterial RNA polymerase, thus blocking mRNA synthesis without affecting the human cells (Blondeau, 1999; Abushaheen et al., 2020).

4. Interference with Metabolic Pathways

Decreased folate cofactors are a prerequisite for many cellular components in both prokaryotic and eukaryotic cells. Tetrahydrofolate is a cofactor required for biosynthetic processes and degradative processes. The folate biosynthetic pathway acts as a target for antibiotics, as both eukaryotic cells and bacteria require folate. Sulfonamides antagonize para-aminobenzoic acid (PABA) for the enzyme dihydropteroate synthase (DHPS), thereby blocking folate synthesis, but dihydrofolate reductase (DHFR), the last step enzyme in folate synthesis, is inhibited by diaminopyrimidine antibiotics such as trimethoprim. Combination therapy of sulfonamides with trimethoprim was a highly successful one but ran into problems because of resistance formation (Fernández-Villa et al., 2019).

5. Disruption of Membrane Integrity

The bacterial cell membrane is critical in maintaining structural stability and regulating permeability. Polymyxins are cationic molecules that bind to the anionic bacterial membranes, causing structural disruption. This interaction causes osmotic imbalance, respiratory inhibition, and finally, cellular death (Moubareck, 2020).

These mechanisms highlight the main strategies used by antibiotics to overcome and treat various bacterial infections.

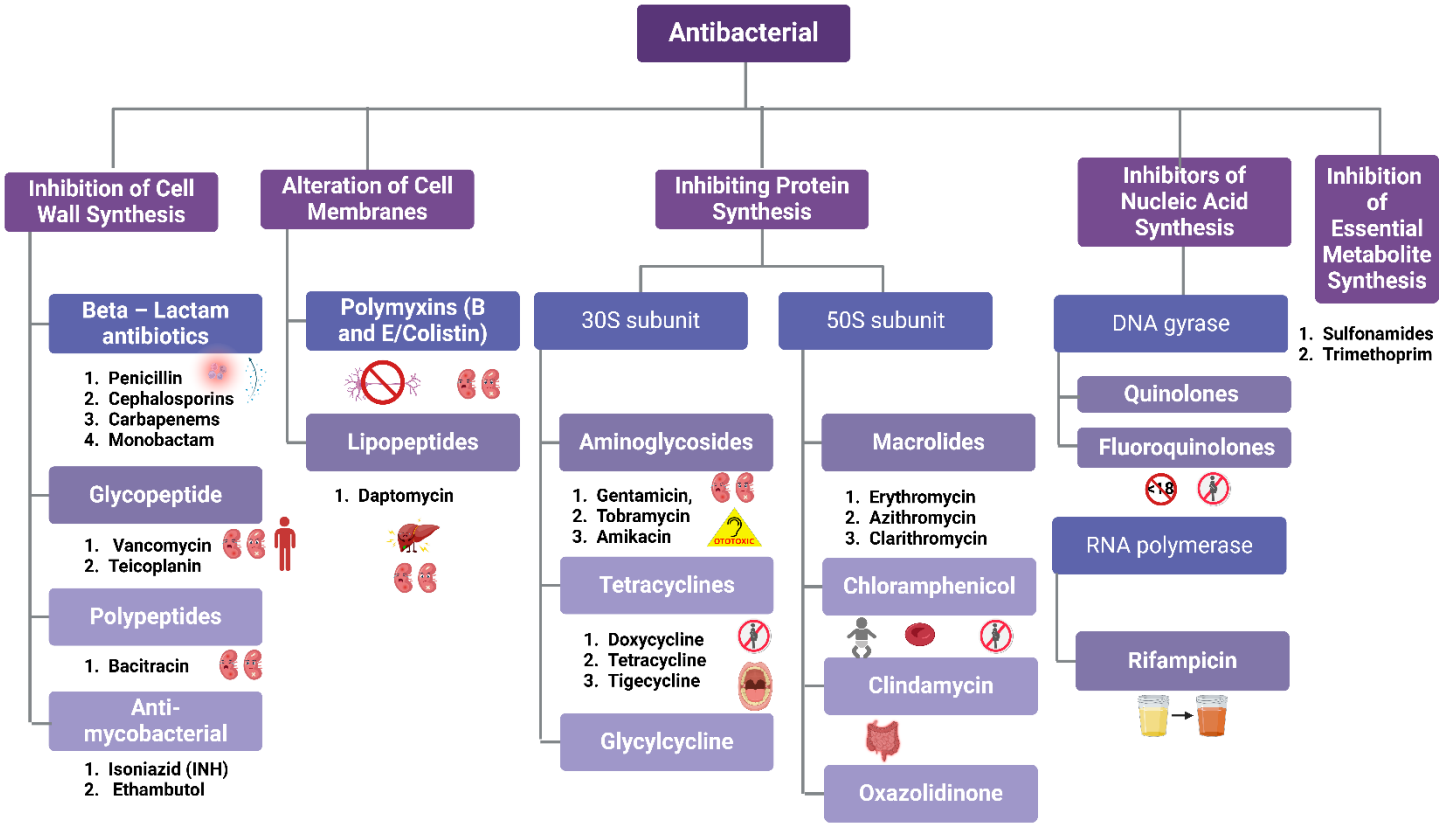

Fig 1. Schematic overview of the major classes of antibacterial agents, classified by their mechanisms of action, along with their most common side effects.

Antiviral Agents and Their Mechanisms of Action

Viruses are responsible for a spectrum of infections ranging in severity and continually represent a major health threat worldwide. Their ability to spread rapidly—sometimes without symptoms—along with their capacity to evolve and evade immune responses or therapies, makes them particularly dangerous. Viral outbreaks can progress to pandemics because of their high transmissibility, globalization, and zoonotic origin. This has been seen in epidemics, e.g., COVID-19 and the 1918 Spanish flu (Kausar et al., 2021). Pandemics generate significant economic and social secondary consequences, in turn straining healthcare provision and disintegrating communities (Burrell et al., 2016). Viruses are obligate intracellular pathogens, and therefore, require invasion into host cells to use host cellular machinery for their replication (Ryu, 2016). The viral particle is quite simple, with a protein capsid, nucleic acids, viral enzymes, and sometimes with a lipid envelop (Goyena and Fallis, 2019). Viral spread and propagate inside the host cell by a process called "virus life cycle" (Coen and Whitley, 2011). Once inside the cell, the virus removes its capsid, transcribes its RNA, begins translating it to viral proteins, replicates its genome, assembles the viral proteins, and then releases from the host cell (Ryu, 2016). Antiviral drugs are used to treat viral infections by targeting different steps in the viral life cycle (**Fig. 2**). These drugs are often virus-specific, and their efficacy can be limited by factors such as toxicity and the development of resistance by the virus. In addition, the treatment outcome with antivirals may differ depending on the participant factors such as genomic or epigenetic reasons, and thus this can limit the effectiveness of drugs. The rationale of use of antiviral drugs relates to the way drugs target the viral life cycle, either by blocking infection or by inhibiting viral load (Kausar et al., 2021), (**Table 1**).

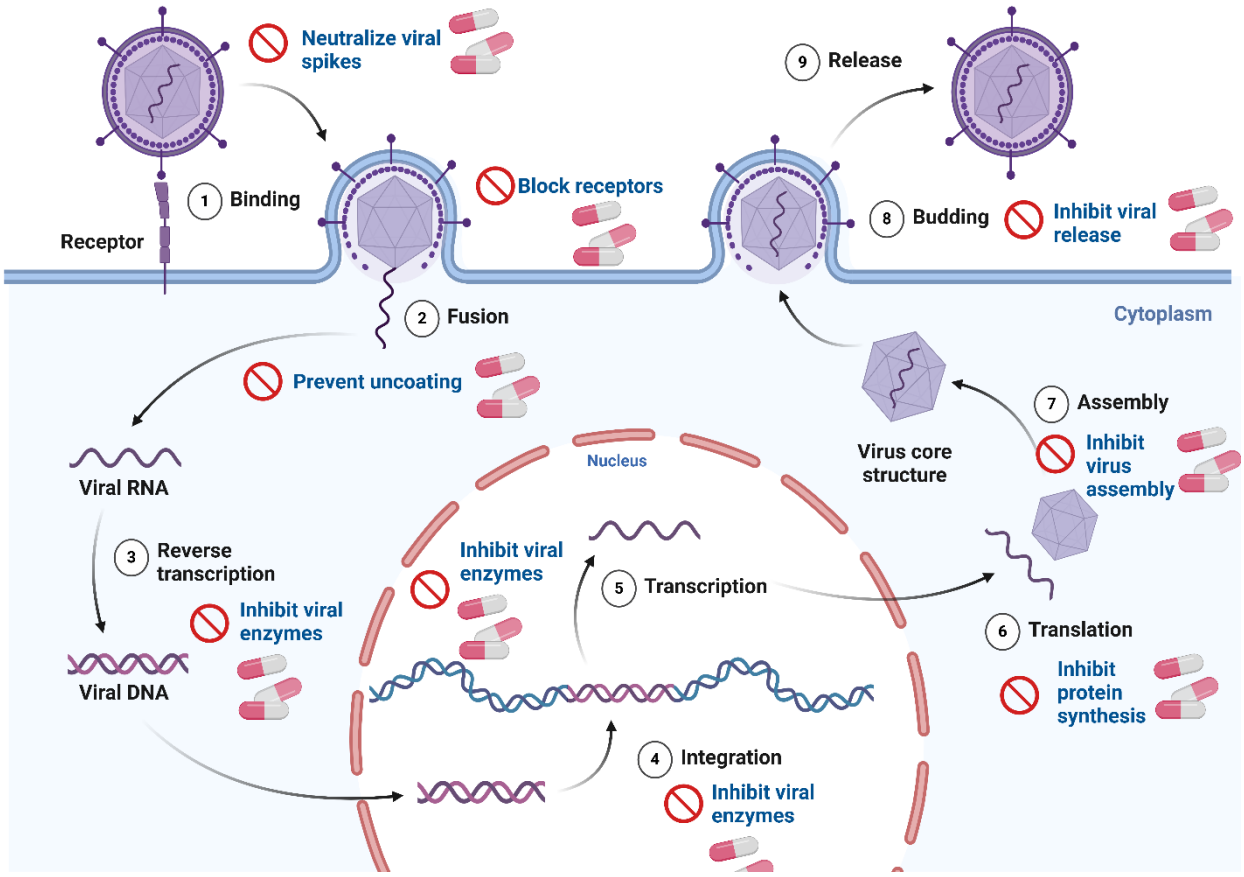

Fig 2. Mechanism of action of antiviral drugs targeting various stages of the viral life cycle, including binding, fusion, reverse transcription, integration, transcription, translation, assembly, budding, and release.

Table 1. Mechanism of action of common antiviral agents (Denyer et al., 2007; Kausar et al., 2021).

Category	Mechanism of action	Example	Target virus
Nucleoside reverse transcriptase inhibitors (nucleoside analogues)	Viral polymerase inhibitors	Abacavir, didanosine, tenofover, lamivudine.	Hepatitis B virus, Herpes virus
Non-nucleoside reverse transcriptase inhibitors	Reverse transcriptase inhibitors	Efavirenz, etravirine, nevirapine.	HIV
Protease inhibitors	Viral protease inhibitors	Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
RNA polymerase inhibitors	RNA polymerase inhibitors	Rifampicin	Ebola
Synthetic amine	Viral uncoating blockers	Amantadine, rimantadine.	Influenza A
Interferons	Induces proteins that inhibit viral replication	Alpha interferon, beta interferon.	Hepatitis B and C viruses
Miscellaneous agents with unique mechanism of action	Integrase Strand Transfer Inhibitor (INSTI). Fusion Inhibitor.	Enfuvirtide, maraviroc, raltegravir.	HIV

The viral replication process can generally be summarized in the following stages:

1. Adsorption of the virus to the host cell and entry.
2. Uncoating to release the viral genome.
3. Synthesis of viral nucleic acid.
4. Integration of viral DNA into the host genome (in the case of latent viruses).
5. Production and assembly of new viral components.
6. Maturation.
7. Release of new virions.

Each of these stages offers a potential intervention point for antiviral therapy (Kausar et al., 2021).

Mechanisms of Action of Antiviral Agents

1. **Inhibition of Viral Entry:** Some antiviral drugs block the virus from entering host cells by targeting viral surface proteins or host cell receptors. For instance, maraviroc (used for HIV) blocks the C-C chemokine receptor type 5 (CCR5) receptor, while enfuvirtide prevents fusion of the viral and cellular membranes.
2. **Uncoating Inhibition:** Drugs such as amantadine and rimantadine inhibit the uncoating process in viruses like influenza A by blocking the M2 ion channel, which is essential for releasing viral genetic material into the host cell.
3. **Inhibition of Nucleic Acid Synthesis:** Several antiviral drugs mimic nucleosides, interfering with the synthesis of viral DNA or RNA. Examples include acyclovir (for herpes viruses) and remdesivir (for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)). These drugs are incorporated into viral nucleic acids, leading to chain termination during replication.
4. **Inhibition of Protein Synthesis:** Some antivirals, like fomivirsen (targeting Cytomegalovirus), inhibit viral mRNA or protein synthesis, preventing the formation of essential viral components.
5. **Assembly and Maturation Inhibitors:** Protease inhibitors like ritonavir (used for HIV) prevent the cleavage of viral polyproteins, which is necessary for the assembly of mature viruses.
6. **Inhibition of Viral Release:** Drugs such as oseltamivir and zanamivir target neuraminidase in influenza viruses, preventing the release of new viral particles from infected cells (Kausar et al., 2021).

Viral challenges present numerous obstacles, including rapid mutation (alterations in genetic material), complex transmission dynamics, and the difficulty in developing effective vaccines (Domingo et al., 2021). Emerging viruses, such as SARS-CoV-2, further complicate detection, treatment, and prevention efforts (Solanki et al., 2023). Host-virus interactions also contribute to varied disease outcomes, complicating immune responses. In addition, controlling the spread of viruses is difficult, particularly with asymptomatic or pre-symptomatic carriers. Developing antiviral drugs that target a broad spectrum of viruses remains a significant challenge. Effective surveillance and global cooperation are essential for mitigating viral threats. Since viruses rely on the host's cells for replication, designing safe and effective antiviral drugs is challenging. Identifying drug targets that disrupt the virus without harming host cells remains a complex task. Moreover, viral variation poses a major obstacle in the development of both antiviral drugs and vaccines (Trovato et al., 2020; von Delft et al., 2023).

Antifungal Agents and Their Mechanisms of Action

Fungal infections affect an estimated 1.7 billion individuals globally, with the highest prevalence among immunocompromised patients, such as those undergoing chemotherapy, living with acquired immune deficiency syndrome (AIDS), or following organ transplantation (Pianalto and Alspaugh, 2016). To combat these infections, antifungal agents form a specialized class of drugs specifically designed to treat mycoses. The effect of antifungal agents can be either fungicidal or fungistatic. The fungicidal action, where fungi are directly killed and the fungistatic action, where fungal growth is inhibited. These mechanisms target vital fungal structures and processes, disrupting their survival and proliferation (Vanreppelen et al., 2023).

Targets of Antifungal Agents and Drug Classes

The primary targets of antifungal agents are three key components of the fungal cell: the cell wall, the cell membrane, and the nucleus, as shown in **Fig 3**. Each of these targets is associated with specific classes of antifungal drugs:

1. **Cell Wall**: Drugs such as glucan synthesis inhibitors act on this structure.
2. **Cell Membrane**: Agents like ergosterol synthesis inhibitors and disruptors target membrane stability.
3. **Nucleus**: DNA, RNA, and protein synthesis inhibitors, as well as mitosis inhibitors, target fungal nucleic acids and cell division (Carrillo-Muñoz et al., 2004).

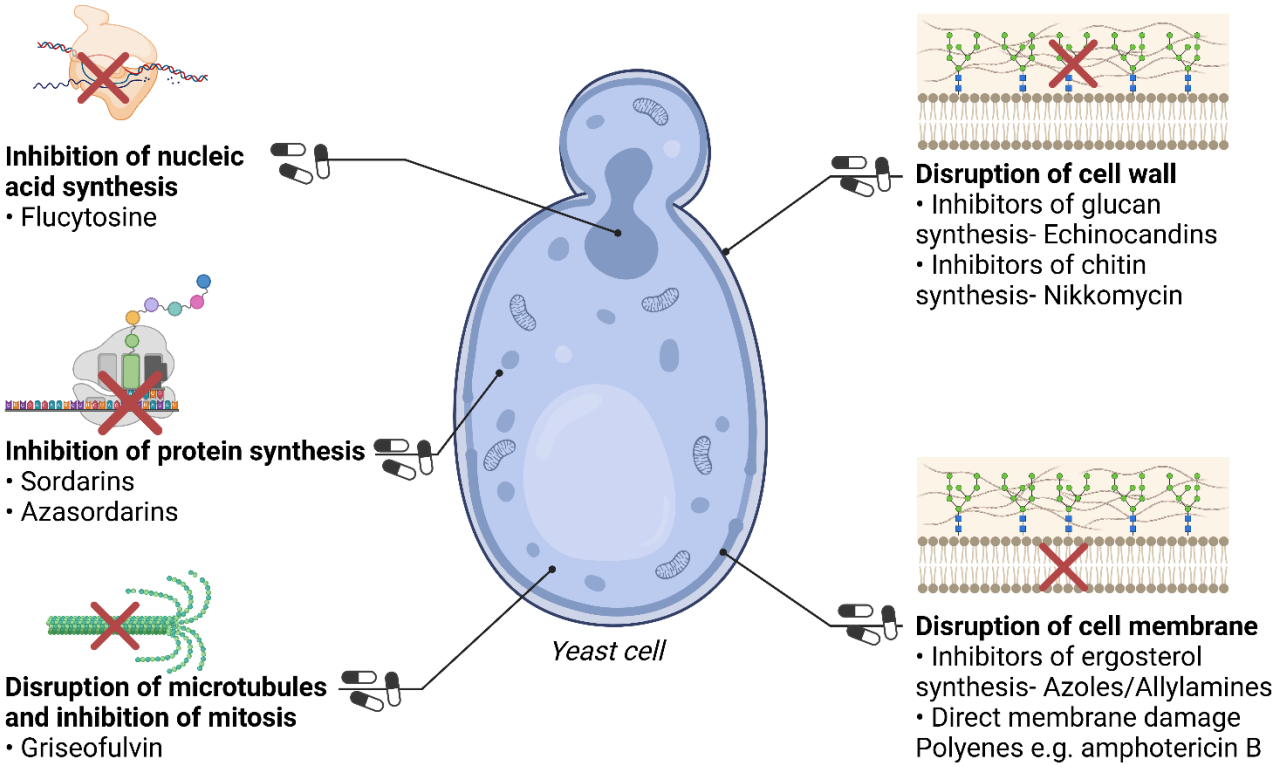

Fig. 3. Mechanisms of antifungal agents targeting key fungal structures, including the cell wall, cell membrane, and nucleus. Adopted from (Murray et al., 2014).

Mechanisms of Action of Antifungal Agents

The fungal cell structure comprises an outer cell wall and an inner cell membrane. The cell membrane consists predominantly of phospholipids and sterol molecules like ergosterol. The biosynthesis of ergosterol begins with squalene, which is converted to lanosterol via the enzyme squalene epoxidase. Lanosterol is subsequently transformed into ergosterol by the action of the cytochrome P450 enzyme 14α-demethylase, found in fungal mitochondria and endoplasmic reticulum. Ergosterol plays a crucial role as a bioregulator of membrane fluidity, asymmetry, and integrity, making it a primary target for antifungal drugs (Ghannoum and Rice, 1999). Without ergosterol, the cell membrane loses its stability and integrity, leading to dysfunction of membrane-bound ion channels and structural rigidity, which leading to inhibition of fungal growth (Tevyashova et al., 2013).

1. Antifungal Agents Targeting the Cell Membrane

1. **Polyenes**: Drugs such as amphotericin B and nystatin bind directly to ergosterol, forming pores in the fungal membrane. This increases membrane permeability, causing leakage of intracellular potassium and other ions, ultimately leading to fungal cell death (Tevyashova et al., 2013).

2. **Azoles**: These agents, including fluconazole, inhibit 14α-demethylase, preventing the conversion of lanosterol to ergosterol. The accumulation of lanosterol disrupts membrane integrity, resulting in fungal cell death (Rosam et al., 2021).

3. **Allylamines**: Terbinafine blocks squalene epoxidase, inhibiting ergosterol synthesis and leading to toxic accumulation of squalene in the fungal cell (Biswas and Thakur, 2024).

2. Antifungal Agents Targeting the Cell Wall

The fungal cell wall is composed of carbohydrates, including β-glucan, a polysaccharide cross-linked with other carbohydrates to provide structural strength.

Echinocandins: This class of drugs (e.g., anidulafungin, caspofungin, micafungin) inhibits 1,3-β-glucan synthase, an enzyme absents in human cells. By preventing β-glucan synthesis, echinocandins compromise the cell wall, rendering it fragile and leading to fungal cell death (Douglas, 2001; Hashemian et al., 2020).

3. Antifungal Agents Targeting the Nucleus

1. **Griseofulvin**: This drug interferes with fungal mitosis by disrupting microtubule function, thereby inhibiting fungal replication (Biswas and Thakur, 2024).

2. **Flucytosine (5-FC)**: Once converted by fungal cytosine deaminase into 5-fluorouracil (5-FU), it is incorporated into fungal RNA, disrupting protein synthesis. Additionally, 5-FU inhibits thymidylate synthase, reducing thymine production and impairing fungal DNA synthesis, ultimately causing cell death (Delma et al., 2021).

Antifungal drugs work by breaking down cell walls, disrupting membrane integrity, or stopping the division and production of nucleic acids in fungi. These are collectively the most effective strategies to combat fungal infections, particularly in immunocompromised patients.

Mechanisms of Bacterial Resistance to Antibacterial Agents

Clinical resistance to salvarsan, the first antibiotic, was first documented in 1924, by *Treponema pallidum*, following its discovery in 1909. Similarly, resistance to penicillin, which was discovered in 1928 and commercialized in the 1940s, reported by *Staphylococcus aureus* in 1942 (Stekel, 2018). By the 1950s and 1960s, resistance had also developed in other bacterial species, including *Salmonella* spp., *Shigella* spp., and *Escherichia coli*. This rapid emergence of resistance continues, as bacteria develop adaptive mechanisms nearly as quickly as new antibiotics are introduced (Aslam et al., 2018). Over the past century, the use of antibiotics has driven the evolution and dissemination of antibiotic resistance genes (ARGs) across bacterial populations globally (Li et al., 2023). These mechanisms include efflux pumps, enzymatic inactivation, target site modifications, resistance-conferring plasmids, altered cell wall structures, and resistance mutations (Li et al., 2023), **Fig 4**.

Mechanisms of Antibiotic Resistance

Efflux pumps

Efflux pumps, protein-based transporters embedded in bacterial membranes, actively expel foreign substances such as antibiotics, detergents, and disinfectants, reducing their intracellular concentrations and preventing them from reaching their targets (Kumar and Schweizer, 2005; Piddock, 2006). These pumps play critical roles in bacterial pathogenesis, metabolism, and multidrug resistance (MDR). Consequently, efflux transporters have become desirable targets for novel inhibitors aimed at combating MDR infections. Based on structure, energy source, substrate specificity, and sequence similarity, efflux pumps are categorized into five superfamilies: ATP-binding cassette (ABC), proteobacterial antimicrobial compound efflux (PACE), major facilitator superfamily (MFS), resistance nodulation division (RND), multidrug and toxic compound extrusion (MATE), and small multidrug resistance (SMR) (Du et al., 2018). While transporters in the MATE, MFS, RND, and SMR families utilize H^+ or Na^+ ion gradients as energy sources to extrude molecules, ABC pumps rely on ATP hydrolysis for their activity (Lubelski et al., 2007; Kim and Hummer, 2012).

Enzymatic inactivation

Bacteria employ enzymatic inactivation to neutralize antibiotics, often targeting their hydrolytically sensitive bonds (e.g., esters or amides). Amidases, for example, cleave the β-lactam ring in penicillin and cephalosporins, rendering these antibiotics ineffective (Wright, 2005). Among resistance determinants, β-lactamases are particularly prominent in Gram-negative bacteria and use two molecular strategies to hydrolyze the β-lactam ring: serine β-lactamases or metallo-β-lactamases (Bush, 2018). Researchers have categorized β-lactamases into four major groups based on structural and functional properties. Groups A, C, and D include active-site serine β-lactamases, while group B is zinc-dependent or metallo-β-lactamases (MBLs). The similarities in catalytic mechanisms between β-lactamases and peptidoglycan transpeptidases suggest an evolutionary relationship, highlighting shared features such as active site Ser residues and nucleophilic attacks (Castanheira et al., 2021).

Target site modifications

Bacteria interfere with antibiotic binding by altering or protecting their target sites. For example, the tetracycline resistance proteins Tet(M) and Tet(O), initially identified in *Streptococcus* spp. and *Campylobacter jejuni*, respectively, are now widespread among various bacterial species (Hoffman, 2001). These proteins, homologous to elongation factors EF-G and EF-Tu, interact with ribosomes to displace tetracycline and prevent it from inhibiting protein synthesis (Dönhöfer et al., 2012; Li et al., 2013). Similarly, mutations in the rifampin binding site of RNA polymerase (encoded by rpoB) reduce the drug's affinity while maintaining the enzyme’s functionality, enabling transcription to proceed despite antibiotic presence (Floss and Yu, 2005).

Antibiotic Resistance in Biofilms

Biofilms, which were first observed by van Leeuwenhoek in the 17th century, represent a significant challenge in treating bacterial infections (Dufour et al., 2010). These microbial communities, often found on medical devices such as catheters and prosthetics, are protected by extracellular polymeric substances (EPS). The

EPS matrix impedes antibiotic diffusion, shields biofilm cells from phagocytosis, and enhances resistance to disinfectants. Consequently, biofilms are responsible for a substantial proportion of hospital-acquired infections (Balducci et al., 2023).

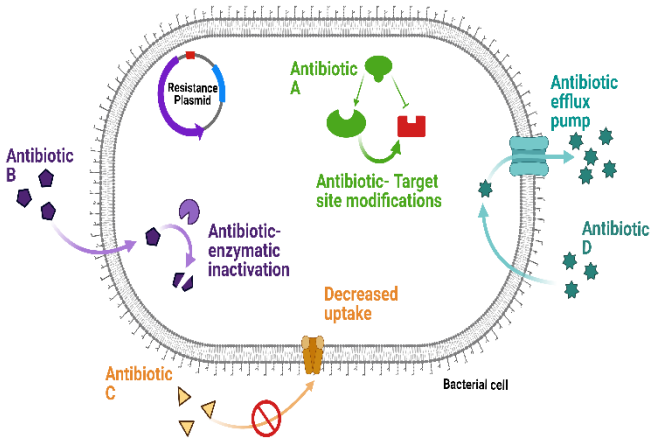

Fig. 4. Overview of bacterial resistance mechanisms against antibacterial agents.

Multiple bacterial resistance constantly emerging to add great barrier in the way of antimicrobial therapy. Over the years, bacteria have acquired various mechanisms to counter antibiotic action, turning them into so-called "superbugs." In order to overcome these challenges, scientists have to focus on alternatives, like the creation of efflux pump inhibitors or antimicrobial peptides. Crucially, the success rate of clinical trials improved by testing new therapeutics on clinically resistant isolates which can improve the effectiveness of treatment strategies (Kabra et al., 2019).

Mechanisms of Viral Resistance to Antiviral Agents

Viruses are the simplest structural entities consisting of a protein coat, containing nucleic acid and, in many instances, an additional lipid bilayer envelope. Despite being completely reliant on host cells for replication, they are inherently resistant to numerous currently available conventional drugs (Goyena and Fallis, 2019). This dependency emerges unique challenges in antiviral drug design, as safe and effective antivirals must target the virus without harming the host cells. The challenge is further complicated by the constant evolution and mutation of viral genomes (Sanjuán and Domingo-Calap, 2016). Antiviral drugs function by inhibiting viral growth rather than directly destroying the virus. Since viruses integrate into host cells and utilize host machinery for replication, this close association makes targeting them without affecting the host particularly difficult. RNA viruses, for example, replicate through reverse transcription, where their RNA genome is transcribed into DNA and integrated into the host genome. In contrast, DNA viruses replicate their genome directly within the nucleus of host cells. Targeting a virus with any drug creates selective pressure that often leads to the emergence of resistant strains. This selective pressure accelerates the rate of viral mutations, which is a key mechanism driving antiviral resistance (Kausar et al., 2021).

Viral mutations

The enzymes responsible for replicating viral genomes are the primary drivers of mutations, and these mutations significantly increase the likelihood of drug resistance. RNA viruses, in particular, demonstrate much higher mutation rates compared to DNA viruses due to the lower fidelity and proof-reading of RNA-dependent RNA polymerases (Coen and Whitley, 2011). Mutations arise through mechanisms such as genetic recombination and random genetic rearrangement. While most mutations are harmful to viruses itself, some enhance genetic diversity and contribute to resistance. Viral mutations can result from replication errors, nucleic acid damage, or genetic modifications during replication and recombination processes (Sanjuán and Domingo-Calap, 2016).

Categories of antiviral agents targeting hiv-1 proteins

HIV-1, an RNA virus, demonstrates remarkable adaptability through mutations, making it resistant to several antiviral therapies. To combat this, five main categories of antiretroviral agents have been developed to target specific viral proteins:

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

These drugs inhibit the viral reverse transcriptase enzyme, thereby preventing the virus from converting its RNA genome into DNA for integration into the host genome.

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Similar to NRTIs, these drugs inhibit the reverse transcriptase enzyme but bind to a different site, disrupting its function.

3. Protease Inhibitors (PIs):

These drugs block the viral protease enzyme, preventing it from cleaving large viral polyproteins into smaller, functional units necessary for viral assembly.

4. Integrase Inhibitors (INIs or INSTIs):

These agents prevent the viral DNA from integrating into the host genome, thereby halting replication at an early stage.

5. Entry Inhibitors:

These drugs block the virus from binding to and entering host cells, thereby preventing infection.

These antiretroviral categories represent key strategies in addressing HIV-1 resistance. However, the continuous emergence of mutations underscores the need for ongoing research to identify new therapeutic targets and refine existing strategies (Trivedi et al., 2020; Temereanca and Ruta, 2023; Mooko et al., 2024).

Mechanism of Fungal Resistance to Antifungal Agents

Globally, fungal infections affect over a billion individuals, causing a range of conditions from superficial and allergic infections to life-threatening diseases (Brown et al., 2012; Bongomin et al., 2017). Currently, only five classes of systemic antifungal agents are available for treatment: polyenes, azoles, echinocandins, allylamines, and 5-flucytosine (Robbins et al., 2017). However, treatment failures are common due to various factors, including host immune deficiencies, inadequate pharmacokinetics, variability in fungal strain characteristics such as cell size, and the development of resistance (Fisher et al., 2018).

Similar to bacterial resistance, fungi develop resistance to antifungal agents through mechanisms that may involve alteration of drug target or unrelated pathways. **Table 2** presents a comparison of the differences and similarities between bacterial and fungal resistance mechanisms. Genetic mutations in key genes, such as those encoding lanosterol demethylase (targeted by azoles) or glucan synthase (targeted by echinocandins), can lead to alterations in target-binding regions, overproduction of the target enzyme, or changes in the drug concentration required for effective inhibition. For instance, excessive efflux of azoles from fungal cells or interference with the activation of prodrugs like 5-fluorocytosine can significantly diminish drug efficacy (Edlind and Katiyar, 2010). Unlike resistance, antifungal tolerance enables certain fungal cells to survive at drug concentrations exceeding the minimum inhibitory concentration (MIC). This phenomenon involves general stress response pathways and epigenetic mechanisms (Berman and Krysan, 2020).

Table 2. Comparison of differences and similarities in resistance mechanisms to antimicrobial agents between bacteria and fungi

Differences		**Similarities**
Bacterial resistance	**Fungal resistance**	
Horizontal gene transfer (HGT) via mobile genetic elements (MGEs).	Limited HGT; resistance spreads primarily through mutations and recombination.	Spread via global travel, trade, and human/animal reservoirs.
Haploid core genome with accessory elements.	Haploid, diploid, or multinucleated cells with complex genomes.	Large-scale antimicrobial/fungicide used in agriculture accelerates resistance.
Resistance develops quickly due to extensive drug use and gene transfer.	Resistance develops slower, linked to fungicide exposure and mutations.	Gene copy number variations contribute to resistance.
Significant role in zoonotic infections and nosocomial outbreaks.	Rising concern with slower spread but high clinical impact (e.g., *Candida* and *Aspergillus*).	Both require optimized pharmacokinetics and stewardship strategies.

1. Genetic Mechanisms of Resistance

The ERG11 gene encodes 14α-demethylase, a critical enzyme in the ergosterol biosynthesis pathway. Mutations, gene conversions, and overexpression of ERG11 contribute significantly to azole resistance. For instance, a point mutation (R467K) in *C. albicans* was found to alter the enzyme's structure, reducing its affinity for fluconazole (Joseph-Horne and Hollomon, 1997; White, 1997; Lamb et al., 2000). Similarly, a T315A mutation, substituting threonine with alanine, affects the active site above the enzyme's heme cofactor, further diminishing azole efficacy. Studies also reveal that overexpression of ERG11 and efflux pumps encoded by CDR1, CDR2, and CaMDR1 contribute to azole resistance, although their roles may vary in clinical isolates (Cannon et al., 2009; Zhang et al., 2019).

2. Efflux Pumps and Resistance

Efflux pumps, such as ATP-binding cassette (ABC) transporters (Cdr1, Cdr2) and major facilitator superfamily (MFS) pumps (CaMDR1), play a central role in azole resistance. These pumps reduce intracellular drug concentrations, thereby decreasing susceptibility. ABC pumps exhibit broad substrate specificity, while MFS pumps confer resistance selectively to fluconazole. Overexpression of efflux pump genes, often regulated by transcription factors like CAP1, is frequently observed in resistant isolates (Denning et al., 1997; Zhang et al., 2019).

3. Resistance to Echinocandins

Echinocandins, lipopeptides that inhibit β-1,3-glucan synthase, are among the newest antifungal agents. They disrupt fungal cell wall synthesis, causing osmotic instability and cell lysis (Tkacz, 1992; Szymański et al., 2022). Resistance to echinocandins typically arises from mutations in the FKS1 gene, which encodes the glucan synthase catalytic subunit. Laboratory studies have demonstrated similar resistance mechanisms in *Saccharomyces cerevisiae* and *C. albicans*. However, echinocandins show limited efficacy against *Cryptococcus neoformans*, likely due to reduced β-1,3-glucan levels in its cell wall and other unidentified mechanisms (Su et al., 2018; Wu et al., 2023).

The emergence of antifungal resistance poses significant challenges to the effective treatment of fungal infections. Genetic mutations, overexpression of drug targets and efflux pumps, and alterations in the ergosterol biosynthetic pathway contribute to resistance in numerous fungal species, particularly *Candida albicans*. Resistance to echinocandins, driven by FKS1 mutations, underscores the need for continuous surveillance and innovative therapeutic approaches. Addressing antifungal resistance requires a multifaceted strategy, including implementation of antifungals stewardship, precise susceptibility testing, and the development of novel drugs with diverse mechanisms of action. Furthermore, the limited efficacy of existing therapies against certain fungi, such as *C. neoformans*, highlights the necessity for further research into alternative pathways and resistance mechanisms. Finally, battling antifungal resistance demands coordinated efforts in molecular research, clinical practice, and public health initiatives. (Feldmesser et al., 2000; Balashov et al., 2006; Hossain et al., 2022).

Emerging Therapeutic Approaches

1. Bacteriophage therapy as a strategy against bacterial resistance

Bacterial viruses, commonly called bacteriophages or simply phages, are viruses that can only infect and replicate inside bacterial cells. That unique property makes them valuable tools for fighting bacterial infections. Phages exist in all natural ecosystems; it has been estimated that they are the most common biological entities on earth. Phages, most prominently known for their overwhelming presence in gut bacterial ecosystems, play a significant role in modulating and maintaining bacterial community dynamics (Jamal et al., 2019). In structure, phages exhibit great diversity, encompassing both tailed and non-tailed types and enveloped and filamentous forms. Their genetic material can be either double-stranded or single-stranded DNA or RNA; still, the most common type found in publicly available databases is that of tailed double-stranded DNA phages (Dion et al., 2020).

Researchers have discovered the therapeutic potential concerning phage therapy. For example, one study found that phages were effective in treating experimental infections of *Klebsiella pneumoniae* in murine models. The findings demonstrated that phages produced similar results to ciprofloxacin, especially in the control of infections initiated by this challenging pathogen. In addition, phages are capable of enhancing the efficacy of antibiotics by reducing the minimal inhibitory concentration (MIC) and acting synergistically with these drugs (Grygorcewicz et al., 2021; Aleshkin et al., 2021).

Phage therapy is gaining increasing attention as a potential alternative to, and adjunct to, conventional antibiotics (Hetta et al., 2023). This approach is especially critical in the battle against antibiotic-resistant microbes, including ESKAPE pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. These pathogens significantly lead to lower respiratory tract infections (LRTIs), including conditions such as acute bronchitis and exacerbations of chronic respiratory diseases. The treatment of LRTIs is usually challenging; however, phage therapy has promising results against these life-threatening health problems (Mahashur, 2018). These infections include conditions such as acute bronchitis and acute exacerbations of chronic respiratory diseases, each presenting unique clinical challenges. A pivotal study demonstrated that phage therapy was effective in treating these critical respiratory conditions (Cui et al., 2024).

Biofilms, the protective structures produced by the bacterial organisms, are yet another major challenge in infection treatment. Biofilm formation is responsible for up to 70% of infections and is commonly reported in scenarios involving medical devices, including central vascular catheters, urinary catheters, and orthopedic implants. Furthermore, tissue infections, such as chronic

otitis and lung infections associated with cystic fibrosis, have also frequently revealed the presence of biofilms (Høiby et al., 2015). The ability of bacteria to form biofilms and exhibit resistance to antibiotics has turned these infections into a major concern for health organizations worldwide (Brooke, 2014). Phages, are a promising approach to combat biofilm-associated infections. They produce enzymes, including depolymerases and lysins, that degrade the EPS matrix biofilms are made of, thereby allowing phages access to bacteria sequestered within the matrix—a haven generally impenetrable to antibiotics (Pires et al., 2016). Phage tail fibers, combined with secreted enzymes, further this process as they break down matrix components and facilitate bacterial clearance (Hughes et al., 1998).

Despite their promise, there are many hurdles to overcome before phage therapy can be incorporated into standard clinical practice. These include regulatory and manufacturing hurdles, as well as biological ones, such as phage resistance and interactions with the immune system (Olawade et al., 2024). To overcome these, improvements in production methods and quality assurance will be needed to ensure that phage preparations are consistent, stable, and safe for use in patients.

2. Traditional Herbal Medicine In Fighting Resistant Pathogens

Plants have been used as therapeutic agents in traditional herbal medicines for their bioactive compounds since ancient times (Pieters and Vlietinck, 2005; Balunas and Kinghorn, 2005a). The World Health Organization (WHO) recognizes traditional medicine as a cost-effective strategy for achieving universal healthcare and encourages countries to incorporate plant-based remedies wisely (World Health Organization (WHO), 1998; World Health Organization (WHO), 2000). The excessive use of high-dose antibiotics to treat localized infections often causes tissue damage and adverse side effects, which can accelerate the development of antibiotic resistance (Walsh et al., 2023). Consequently, plant-based therapies have gained increasing attention as complementary or alternative treatments for emerging infectious diseases (Valli et al., 2012). Medicinal plants contain diverse bioactive compounds, including coumarins, flavonoids, phenolics, alkaloids, terpenoids, tannins, essential oils, lectins, polypeptides, and polyacetylenes, many of which serve as templates for developing new antimicrobial agents (Edeoga et al., 2005; Górniak et al., 2019; El-Fakharany et al., 2023; El-Fakharany et al., 2024), **Table 3**.

Examples of plant-based antimicrobial compounds

Garlic's active compound, allicin, effectively combats a wide range of bacteria, including those causing periodontitis and antibiotic-resistant strains such as MRSA (Lanzotti et al., 2014). Studies have shown that allicin enhances the efficacy of antibiotics such as cefoperazone, tobramycin, and ciprofloxacin against *Pseudomonas aeruginosa* (Davis, 2005). Allicin's antimicrobial effects are attributed to its inhibition of enzymes, including alcohol dehydrogenase, thioredoxin reductase, and RNA polymerase, which depend on sulfhydryl groups (Bhattacharya et al., 2022). The interaction of allicin with cysteine and glutathione reduces its inhibitory effects, suggesting a mechanism involving sulfhydryl reactivity. Additionally, allicin interferes with DNA and protein synthesis and may also impact RNA synthesis (Bhattacharya et al., 2022).

Ajoene, another garlic-derived compound, exhibits strong antimicrobial properties against bacteria, fungi, and protozoa, and it demonstrates antiviral activity exceeding that of allicin (Rehman and Mairaj, 2013). Similar to allicin, ajoene's activity is reduced in the presence of cysteine, indicating a shared mechanism that targets thiol-dependent enzyme systems (Nguyen et al., 2013).

Piperine, an alkaloid found in black and long pepper, enhances the efficacy of antibiotics. When combined with ciprofloxacin or gentamicin, it inhibits the growth of *S. aureus*, lowers MIC values, and effectively combats MRSA infections by interfering with the NorA efflux pump (Stojanović-Radić et al., 2019; Zahin et al., 2021).

Thymol, a monoterpenoid phenol, demonstrates significant activity against *Candida albicans*, *C. glabrata*, and *C. krusei*, either alone or in combination with fluconazole, achieving MIC values of 49.37, 51.25, and 70 μg/mL, respectively (Althunibat et al., 2016). Furthermore, thymol, in combination with carvacrol, eugenol, and menthol, exhibits synergistic antifungal effects with fluconazole and shows efficacy against fungi responsible for food spoilage, presenting viable alternatives to synthetic fungicides (Althunibat et al., 2016).

Capsaicin, the active component of chili peppers (8-methyl-N-vanillyl-trans-6-nonenamide), exhibits antimicrobial activity by disrupting the bacterial cell wall in pathogens such as *E. coli* and *Streptococcus mutans*. Additionally, capsaicin has shown potential antiviral activity against SARS-CoV-2 by binding to the viral 3C-like protease and inducing structural changes in the virus (Akyuz et al., 2018; Jo et al., 2020). Red ginger contains monoterpenes as its primary antimicrobial agents, with β-caryophyllene identified as the major compound exhibiting potent antimicrobial activity (Sivasothy et al., 2011).

Table 3. Antimicrobial activities of some bioactive compounds from traditional herbs

Family	Scientific name (Common name)	Compound	Effective in Combating	References
Amaryllidaceae	*Allium sativum* (**Garlic**)	Allicin, ajoene	General antimicrobial	(Pieters and Vlietinck, 2005)
Apiaceae	*Syzygium aromaticum* (**Clove**)	Eugenol	General antimicrobial	(Alanazi et al., 2022)
Piperaceae	*Piper nigrum* (**Black pepper**)	Piperine	Fungi, *Lactobacillus*, *Micrococcus*	Piperaceae (Balunas and Kinghorn, 2005b)
Solanaceae	*Capsicum annuum* (**Red pepper**)	Capsaicin	*E. coli*, *Streptococcus mutans*, SARS-CoV-2	(Akyuz et al., 2018)
Zingiberaceae	*Zingiber officinale* (**Ginger**)	B-caryophyllene	Anti-gram negative Anti-gram positive	(Sivasothy et al., 2011)

Future research should prioritize the identification and development of plant-derived secondary metabolites as potential treatments for infectious diseases. Combining natural compounds from various sources with existing antibiotics presents a promising strategy to combat resistant pathogens and mitigate the growing impact of antimicrobial resistance (Khameneh et al., 2019; Abo Nouh et al., 2021; Angelini, 2024).

Conclusion, Challenges and future perspective

Tackling AMR is significant challenges that impact the global health. The primary cause of this crisis is the overuse and misuse of antimicrobial agents in humans, animals, and agriculture. These issues are compounded by other factors that contribute to the spread of resistance. For example, inadequate sanitation, the scarcity of rapid and sensitive diagnostic tools —particularly in low- and middle-income countries—and limited global surveillance exacerbate the problem. Moreover, the economic disincentives for pharmaceutical companies to invest in the development of novel antimicrobial agents. To counter these challenges, rising public awareness and implementing antimicrobial stewardship should become an obligatory priority for policymakers rather than an option. Additionally, greater efforts are needed to achieve the goals of the "One health" approach, which emphasize the integration and interconnection of human, animal, and ecosystem. Lastly, increased funding should be allocated to combat antimicrobial resistance, with the focus on advancing research to develop new antimicrobials and vaccines.

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