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Mechanisms, Dissemination, Determinants, and Alternate Strategies for Addressing Antibiotic Activity and Resistance

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REVIEW ARTICLE

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ABSTRACT

The use of antibiotics is a commonly used therapeutic approach for the treatment of bacterial diseases in a variety of fields, such as human health, agriculture, cattle breeding, and fish aquaculture. How well antibiotics work depends on four different mechanisms of action, each of which is covered in detail in this review. Antibiotic resistance has become a major obstacle to treating bacterial illnesses, notwithstanding its effectiveness. Antibiotics are no longer effective because bacteria have evolved resistance mechanisms against them. There are several ways that antibiotic resistance can develop among bacteria, making previously vulnerable microorganisms resistant to antibiotics. The abuse of antibiotics by humans is one of several causes contributing to the growing antibiotic resistance dilemma. Alternative strategies put forth to lessen the escalation of antibiotic resistance are also highlighted in this review.

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Introduction

In microbiology, the term "antibiotic" was created from the French terms "antibiose" and "antibiotique," which Vuillemin defined in the late 1800s to refer to substances that negatively affect living organisms, particularly microorganisms [1]. Antibiotics are used extensively in a variety of fields, including agriculture, fish farms, human health, and cattle breeding. Four different methods of action—inhibition of DNA replication, protein production, cell wall biosynthesis [2], and folic acid metabolism [3] underlie the effectiveness of antibiotics [4]. But the rise in antibiotic resistance has become a serious worldwide concern [5].

Usage of Antibiotics

Numerous fields, including human health, animal husbandry, aquaculture, and agriculture, use antibiotics. In order to prevent crop loss due to bacterial diseases, these compounds are used to treat bacterial infections in humans, animals, and crops [6]. Antibiotics are also frequently employed in animal husbandry as growth-promoting drugs [7]. Scientists divide the use of antibiotics in livestock into three groups: growth promoters, preventive agents, and therapeutic medicines [8]. To treat diseases, huge dosages of therapeutic medicines are given to diseased animals [9]. However, when there are no overt signs of infection, prophylactic medicines are administered at sub-therapeutic doses through food or drinking water to prevent illness [10]. Animals are given antibiotics on a regular basis

during their life cycles. A small amount of antibiotics is routinely given to the animal through its diet, and growth boosters are utilized to increase the animal's growth rate and productivity. Antimicrobial agents are used to treat fish diseases in aquaculture. Antibiotics are administered to fish by mixing them with specially prepared diet, and they mostly release them into the environment. It's important to remember that over 75% of the antibiotics given to fish end up in the water [11].

Rise of Antibiotic Resistance

The CEO of the World Health Organization (WHO), Dr. Tedros Adhanom Ghebreyesus, has cautioned that the worldwide antibiotic resistance epidemic is a serious threat to a century of the accomplishment of sustainable development goals and advancements in healthcare. Current projections indicate that nearly all bacteria will be resistant to the majority of antibiotics used in treatment within 25 years [12]. Additionally, experts estimate that by the middle of the twenty-first century, the number of deaths from antimicrobial resistance could increase from the present annual total of over 700,000 to 10 million [13].

The WHO suggested rating the bacteria with the highest trend in resistance in 2017 in response to this concerning circumstance. On this list are Pseudomonas aeruginosa, Acinobacter baumannii, Salmonella species, Campylobacter species, Helicobacter pylori, Nisseria gonorrhoeae, Staphylococcus aureus, Enterobacteriaceae, and Enterococcus fecium. These microorganism species are less vulnerable to antibiotic therapy because of their strong resistance to several kinds of antibiotic treatments [14].

Mechanisms of Antibiotic Resistance

Three main strategies are used by bacteria to offset the effects of antibiotics. The following is an outline of these mechanisms [15].

Bacteria stop the build-up of antibiotics in their cells

Bacteria limit the entry of antibiotics into their cells. The outer membrane of gram-negative bacteria possesses porin channels [16]. These channels serve as gatekeepers, limiting the entry of specific antibiotics, such as quinolones and B-lactams, into the bacterial cell. Consequently, fewer bacterial porins may prevent these antibiotics from entering the cell, which could result in higher medication resistance [17].

The cytoplasmic membrane of bacteria contains efflux pumps, which are essential for preserving the equilibrium of solutes within bacterial cells. Nevertheless, by removing medications from bacterial cells before they can reach their intended targets, these pumps can lead to antibiotic resistance [18].

Interestingly, it has been discovered that efflux systems confer resistance to every class of antibiotic, with the exception of polymyxin [19]. Expanding our knowledge of the processes behind efflux systems might offer fresh approaches to the fight against antibiotic resistance.

Bacteria alter the antibiotic's target chemical

Antibiotics are designed to target specific molecules, but even the slightest alteration can prevent their binding, leading to the emergence of antibiotic resistance [5]. By an alteration in the ribosomal 30S or 50S subunits, bacteria can gain resistance against medications that interfere with protein synthesis [2]. Antibiotics including aminoglycosides, tetracycline, macrolides, chloramphenicol, lincosamides, and streptogramin exhibit this kind of resistance [19].

Penicillin-binding proteins (PBPs) are transpeptidase enzymes that are essential for cross-linking peptidoglycan precursors during bacterial cell wall biosynthesis. Since these enzymes are the main targets of βlactam antibiotics, any modifications to their structure or function may result in bacterial resistance to these medications [2].

The enzymes DNA gyrase and topoisomerase are involved in DNA replication [20]. These two enzymes are primarily targeted by quinolone antibiotics, which is why bacterial resistance to quinolones may result from structural changes in them [21]. D-alanyl-D-alanine is a dipeptide residue found in peptidoglycan precursors that is essential for the development of cell walls [18].

Although the ribosomal 30S subunit is known to be the target of tetracycline antibiotics, the ribosome contains defense mechanisms that can withstand their effects [16].

An antibiotic called rifampicin is frequently used to treat bacterial infections. It functions by attaching itself to the DNA's beta-subunit and preventing bacteria from synthesizing RNA dependent enzyme, RNA polymerase. Because of this interaction, the enzyme is unable to efficiently convert DNA into RNA, which inhibits bacterial growth and eventually results in cell death [22]. However, changes in the RNA polymerase enzyme can cause bacteria to become resistant to rifampicin. Resistance to rifampicin may be conferred by mutations in the rpoB gene, which codes for the beta-subunit of RNA polymerase. These alterations may decrease the antibiotic's capacity to suppress RNA production by altering the binding affinity between rifampicin and the RNA polymerase enzyme [23].

Changes in the RNA polymerase enzyme that cause resistance to rifampicin can have a number of effects. The change in peptidoglycan precursor levels is one of the consequences which are crucial parts of the bacterial cell

wall. Variations in these precursors' levels may have an effect on the stability and integrity of the cell wall, which may alter the bacteria's susceptibility to other antibiotics like beta-lactams [23].

It is crucial to remember that changes in the RNA polymerase enzyme are only one of the many ways that rifampicin resistance might develop. Additional processes include the overexpression of efflux pumps, which can actively remove rifampicin from the bacterial cell, and the horizontal gene transfer of resistance genes [22].

Bacteria use enzymes to inactivate antibiotics

Antibiotic inactivation is carried out by three key enzymes. These bacterially generated enzymes are capable of degrading all B-lactam antibiotics that are bound to esters and amides. As a result, bacteria that are able to manufacture beta-lactamase enzymes become resistant to beta-lactam antibiotics [19].

It is well known that enzymes are essential to antibiotic resistance.

In particular, it has been discovered that enzymes such aminoglycoside-modifying enzymes (AMEs) stop aminoglycoside antibiotics from attaching to their ribosomal target. Numerous bacterial strains, such as E. faecalis, S. aureus, and S. pneumoniae, have these enzymes. These enzymes help to confer resistance to aminoglycosides and fluoroquinolones in addition to inhibiting antibiotic adhesion [16]. Because it poses a serious threat to the effectiveness of these antibiotics in treating bacterial infections, the existence of AMEs in bacterial strains is therefore a key concern in the field of antibiotic resistance.

Chloramphenicol is modified by enzymes called as chloramphenicol-acetyltransferases, which acetylate its hydroxyl group, changing the antibiotic so that it can no longer bind to its ribosomal target. As a result, bacteria that have the enzyme chloramphenicol acetyltransferase are resistant to chloramphenicol antibiotics, making them less effective [24].

Antibiotic resistance spreading among microorganisms

A microbe is deemed resistant when it can endure at an antibiotic concentration that would typically inhibit or kill other organisms of the same species [2]. The words "susceptible" and "resistant" are frequently used in clinical practice to characterize the possibility of an antibiotic therapy being successful [5]. When a patient cannot reach the concentration of antibiotic required to inhibit or kill the bacteria, resistance is more likely to develop. Microorganisms may be resistant to antibiotics by nature or develop it following exposure [25]. Resistance can be created by mutations in genes or by the direct transfer of resistance genes, which can be carried on plasmids (mobile genetic elements) and spread by conjugation, transformation, or the transfer of similar DNA by bacteriophages, a process known as transduction [26].

Genetic material, including antibiotic-resistant genes, can spread quickly even among bacteria of different species [5]. Heavy metals and biofilm formation have been shown to accelerate the spread of antibiotic resistance in bacteria. Different resistant bacteria can spread and perhaps cause diseases in different environments because they can travel in a variety of ways. There are a few basic ways that resistant bacteria might spread, though the precise modes of transport may differ based on the bacterium and the surroundings.

Through intimate touch, resistant bacteria can be directly transferred from one person to another. This can happen by respiratory droplets released when an infected person coughs or sneezes, or through physical contact, such as touching or shaking hands with an infected person [27].

On surfaces, resistant bacteria can endure for long periods of time. A person can spread the bacterium to their hands by touching infected surfaces like doorknobs, counters, or medical equipment. The bacteria can then enter their body and perhaps cause an infection if they touch their lips or face. The spread of resistant bacteria can occur most frequently in hospitals and other healthcare settings. The close proximity of patients, inadequate infection control measures, and poor hygiene habits are some of the factors that might lead to the spread of bacteria. If appropriate hand hygiene and infection control procedures are not followed, healthcare personnel may unintentionally transfer resistant germs from one patient to another [28].

Additionally, people can contract resistant germs from animals. Direct contact with infected animals or ingestion of tainted food products, like meat or dairy products, can cause this. Because antibiotics are used in agriculture, farm animals, in particular, might carry bacteria that are resistant to them [29].

Animals can also spread resistant bacteria to humans. This can be brought on by eating contaminated food, such as meat or dairy products, or by coming into close contact with sick animals. Farm animals in particular may harbor bacteria resistant to antibiotics due to their use in agriculture [27].

It is crucial to remember that different bacteria and environments can have different unique modes of movement and transmission. Furthermore, factors including inadequate sanitation, poor hygiene, and subpar infection control procedures can all contribute to the emergence of resistant bacteria [28].

Factors influencing antibiotic resistance

Underuse, overuse, or inappropriate use of antibiotics accelerates the evolution of antibiotic resistance. A number of factors contribute to the indiscriminate use of antibiotics, which fuels antibiotic resistance [2]. These include patients' noncompliance with treatment and demand, prescribers' irrational use of antibiotics in human medicine, drug advertising, dispensing physicians, antibiotic use in agriculture, low-quality antibiotics, insufficient surveillance, and susceptibility testing. Doctors and prescribers may be greatly swayed by patient demand even when they are aware of the patient's condition, which may lead to antibiotic and antimicrobial resistance [5].

Once they start feeling better, patients may stop their therapy, forget to take their medications, or just buy a fraction of their medication. In these situations, more interaction between the doctor and the patient is frequently required to guarantee appropriate treatment compliance. Antibiotics can also be easily obtained at pharmacies without a prescription, which encourages individuals to abuse them [30].

Through promotion, the pharmaceutical sector also contributes to the abuse of antibiotics. For instance, some ads assert that the best course of action for individuals who are at risk is to use specific antibiotics, like ciprofloxacin [31]. In the past, Philippine commercials promoted the use of clindamycin for upper respiratory tract infections and lincomycin for pharyngitis/tonsillitis, even though these illnesses are frequently brought on by viral infections that don't need antibiotics [32]. All things considered, patients, healthcare professionals, and the pharmaceutical business must work together to address the complex problem of improper antibiotic usage.

Medical practitioners have a big influence on how bacteria develop antibiotic resistance [33]. When narrow-spectrum antibiotics might be more suitable, doctors frequently prescribe broad-spectrum ones. Doctors' prescribing practices might differ, and research has indicated that between 30% and 60% of patients are given more antibiotics than are required [34]. Furthermore, there is a serious risk from improper prescriptions and advice from inexperienced medical personnel. According to a related study, private practitioners frequently write prescriptions for needless drugs [35].

A major factor in the emergence of antibiotic-resistant microbes is hospitals and clinics. Insufficient infection control measures, including not washing hands and frequent glove changes have been found to be contributing contributors to this issue. Another problem is the use of subpar antibiotics [5]. The use of outdated and fake antibiotics is a result of this issue, which continues because of a lack of quality compliance and monitoring. Another issue is the improper use of antibiotics in animals. Animals are given certain antibiotics to promote growth and stave against illness. Nevertheless, surveillance and antibiotic susceptibility testing are inadequate [35].

Alternative techniques to combat antibiotic resistance

We are putting people in danger due to the ongoing worldwide antibiotic resistance epidemic. Thus, we ought to concentrate on figuring out how to combat this crisis of resistance.

The following are some strategies to combat this dilemma that we cover in this review article:

Discovering novel antibiotics

Teixobactin, a novel antibiotic that showed bactericidal action against S. aureus, Clostridium difficile, and Bacillus anthracis, was discovered by researchers in 2015. Researchers released an article titled "A Deep Learning Approach to Antibiotic Discovery" in Cell on February 20, 2020 [36]. They found a novel antibiotic named halicin using artificial intelligence that had bactericidal effectiveness against a wide range of resistant and harmful bacteria [37]. The article "Computational identification of a systemic antibiotic for Gram-negative Bacteria" was published in Nature Microbiology on September 26, 2022. They found a novel antibiotic named dynobactin through computational screening, and it showed strong bactericidal action against harmful Gram-negative bacteria that were resistant to conventional antibiotics [38].

The difficulties and constraints encountered in the search and development of novel antibiotics are referred to as the dysfunctional R&D market for identifying new antibiotics. These difficulties include financial, legal, and scientific impediments that prevent the development of potent antibiotics to treat bacterial illnesses. The following are some of the main problems with the broken R&D market for finding new antibiotics:

- Limited financial incentives: Pharmaceutical companies have not invested in researching new antibiotics due to their high cost and limited profitability [39].
- Long development timelines: Companies find it less appealing to invest in this field due to the drawn-out and costly process of creating new antibiotics [39].
- Strict regulatory requirements: The lengthy and intricate regulatory approval process for new antibiotics causes delays in the release of new medications onto the market [40].
- Limited advice on clinical trial design: The development process may be further hampered by the absence of precise recommendations for conducting clinical studies for antibiotics [40].

Table 1. Antibiotic resistance-causing variables in several industries and some suggested remedies for them

Sector	Reasons for Antibiotic Resistance	Suggested Solution
Human Health	Antibiotic prescriptions and usage for viral diseases, such as the common cold, tonsillitis, pharyngitis, influenza, and upper respiratory tract infections [48]	Antibiotics shouldn't be prescribed by doctors for viral illnesses.
	Patients are stopping their therapy when they feel better and not taking the full course of antibiotics [31]	Even if they feel better, patients should continue taking antibiotics for the duration of their prescribed course.
	Patients' self-medication and abuse of antibiotics due to their easy access at pharmacies and ability to purchase them without a prescription [49]	Prohibiting the unprescription sale of antibiotics at pharmacies.
	Doctors overprescribe unnecessary antibiotics, particularly broad-spectrum antibiotics [33]	Only the antibiotics required for the illness should be prescribed by doctors; no extraneous ones should be.
	Inadequate infection control procedures, such as hand washing and glove changing, at clinics and hospitals [50]	Developing infection control procedures in clinics and hospitals should get careful consideration.
	Antibiotics that are outdated or counterfeit are used in hospitals and clinics due to a lack of quality compliance and monitoring [51]	To stop the use of stale and fake antibiotics, hospitals and clinics should pay close attention to quality compliance.

- Antibiotic resistance: Developing new antibiotics is significantly hampered by the emergence of germs that are resistant to them [40].
- Limited knowledge of bacterial biology: Despite advancements in genomics and other technologies, much more has to be discovered about the biology of bacteria and how they develop resistance [40].

Antibiotic Adjuvants

Antibiotic adjuvants are substances that increase the efficacy of antibiotics by preventing resistance mechanisms in bacteria rather than killing them directly. Beta-lactamase inhibitors, for instance, are small-molecule antibiotic adjuvants. For more than 30 years, beta-lactamase inhibitors have been used effectively to treat both Gram-positive and Gram-negative infections when paired with beta-lactam antibiotics. Their application has been well documented [41].

Nano-antibiotics

The use of nanotechnology for the production of pure antibiotic molecules ranging in size from 1 to 100 nm or antibiotic molecules physically affixed to nanoparticles is known as nanoscale antibiotics. Through nanoscale reengineering of antibiotics, this novel antimicrobial strategy revitalizes the current drug portfolio by rendering them efficacious against a range of clinically significant pathogens. Nanoantibiotics are more potent and have distinct physicochemical characteristics from their counterparts [42].

One advantageous application of nanotechnology is the cre ation of nanoscale antibiotics, which are made up of pure a ntibiotic molecules that range in size from 1 to 100 nm or a ntibiotic molecules that are physically affixed to an antibiotic administered via or integrated into nanoparticles at the same dose has noticeably stronger inhibitory effects on bacterial growth because nanoscale drug delivery systems can transport and bind to intracellular targets, lowering bacterial growth and metabolism and ultimately leading to cell death [43].

Botanicals

Alkaloids, flavonoids, phenolics, quinones, tannins, terpenes, coumarins, lectins, and saponins are examples of secondary metabolites that are produced by plants. Numerous pathogens are susceptible to the antibiotic activity of these secondary metabolites [44].

Bacteriophages

The National Institutes of Health (NIH, 2014) claims that bacteriophages are novel components that may be used to counteract microbial resistance [45]. Bacteriophages have been used in numerous trials to treat bacterial diseases in both humans and animals, with encouraging and successful outcomes. Shigella dysenteriae, Vibrio cholera, P. aeruginosa, C. difficile, Vancomycin-resistant E. faecium, β-lactamase-producing E. coli, imipenem-resistant P. aeruginosa [46], Acinetobacter baumannii, E. coli, MDR-S. aureus, unclassified bacterial dysentery, S. typhi, and antibiotic-resistant P. aeruginosa are some of these bacterial pathogens [47]. Table 1 shows the causes of antibiotic resistance in healthcare sector and some suggested solutions for them.

Conclusions

This review article has covered a number of topics pertaining to medications, their modes of action, the problem of antibiotic resistance as well as possible ways to overcome it. Although antibiotics are used in many different fields, their use is still contentious owing to resistance concerns. Antibiotics work by way of four primary mechanisms to kill or inhibit the growth of bacteria. However, bacteria have developed defense mechanisms against antibiotics, diminishing the effectiveness of these drugs. Given the limited capacities of conventional antibiotics due to resistance, we discussed several promising alternative approaches, including the discovery of antibiotic adjuvants, novel antibiotics, and nanoparticle-based bacteriophages, botanicals, and antibiotics. Although developing new antibiotics can be challenging, a combination of complementary techniques could help address the crisis of resistance.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1
	Design of the work, OR	2,5,6
	Data acquisition, analysis, or interpretation	3,4
2. Drafting or reviewing	Draft the work, OR	1,2,5
	Review critically for important intellectual content	3,4,6
3. Final approval	Approve the version to be published	1,2,3,4,5,6
4. Accountable	Agree to be accountable for all aspects of the work	1,2,3,4,5,6

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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