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THE EVOLUTION OF ANTIBIOTICS AND THE RISE OF RESISTANCE

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ABSTRACT
Antibiotics are essential medications used to treat bacterial infections by either killing bacteria or inhibiting their growth. However, the emergence of antibiotic resistance poses a significant threat to public health, rendering many existing treatments ineffective. This resistance arises from factors such as the overuse and misuse of antibiotics in both healthcare and agriculture, as well as inadequate infection control practices. The consequences of antibiotic resistance include increased morbidity and mortality, prolonged hospital stays, and rising healthcare costs. Addressing this challenge necessitates a comprehensive strategy that includes responsible prescribing, public education, improved hygiene practices, and continued research into new antibiotics and alternative therapies. Urgent action is required to preserve the efficacy of antibiotics and ensure effective treatment for bacterial infections in the future.

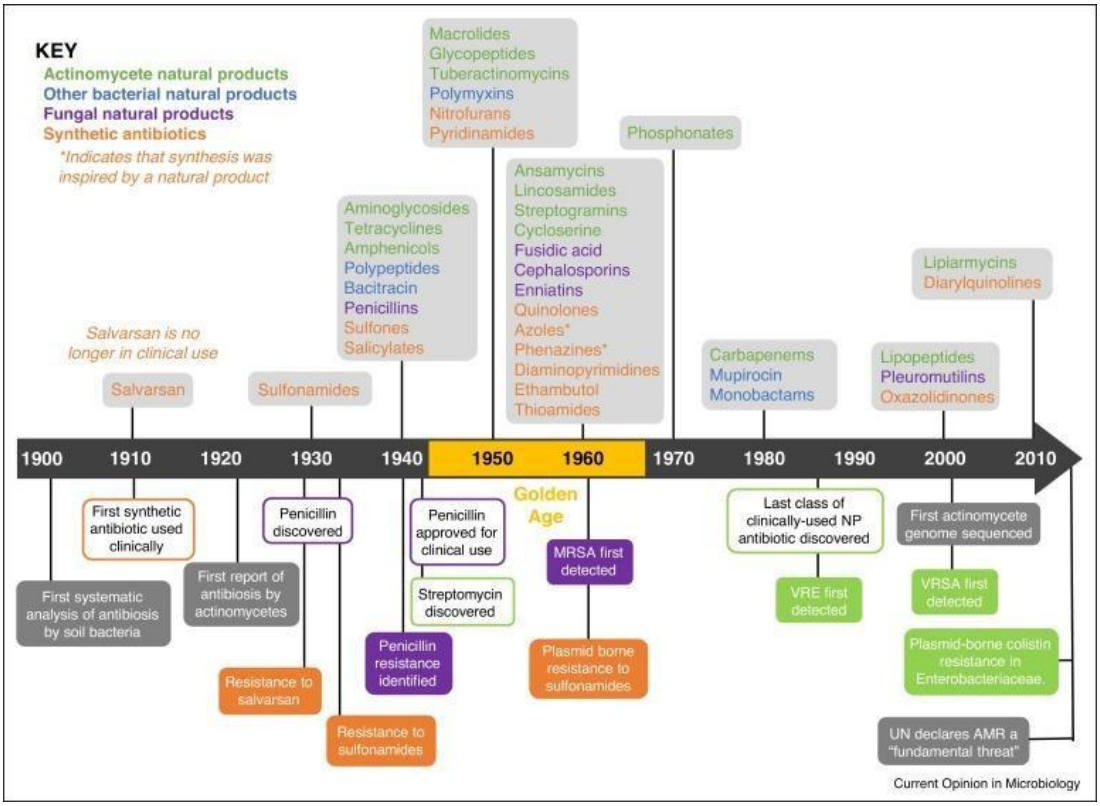
INTRODUCTION

Each year, hundreds of thousands of deaths are caused by bacteria that are widely resistant to antibiotics. The biggest issue is the steadily rising number of microorganisms that are resistant to standard antibiotics, even last- resort medications like vancomycin. The alarming increase in a problem that impacts public health globally and necessitates international cooperation is confirmed by the pace at which resistance genes can spread throughout the world (Supplementary Table S1). In 2014, the World Health Organization (WHO) acknowledged the massive rise in multi-drug resistant strains that has been seen globally as a serious danger to global health.[1]

HISTORY OF ANTIBIOTIC

Perhaps the biggest The creation of antibiotics for therapeutic use was the 20th century's greatest medical advancement.[2] In addition to treating infectious disorders, antibiotics also enabled a number of contemporary medical operations, such as open heart surgery, organ transplants, and cancer treatment. However, improper usage of these beneficial substances has led to the fast increase in antimicrobial resistance (AMR), making certainillnesses practically incurable.[3]

Antibiotic discovery and development is increasingly gaining more attention as a result of legislators' recognition of the threat to human health posed by the post-antibiotic age and their pledge of greater grant financing.[4] By 2050, 10 million people annually may perish from drug-resistant illnesses if immediate action is not taken, according to the O'Neill report, which was commissioned by the UK Government.[5] Promoting early-stage drug discovery is one of the main suggestions.[5] The best chance for creating a new generation of anti-infective medications is to find new microbial natural products (NPs), as these substances are unparalleled in their chemical diversity and efficacy as antibiotics[1], especially considering the relative failure to bring effective synthetic antibiotics to the clinic.[6] The remaining NP antibiotic groups are produced by various bacteria and fungi, with filamentous actinomycetes accounting for 64% of the total. The history of NP antibiotics is briefly reviewed here, along with our chances of finding, creating, and protecting a new class of antibiotics.



Traditional moldy bread poultices were used to treat open wounds in Serbia, China, Greece, and Egypt over 2,000 years ago, demonstrating the long history of using bacteria that produce antibiotics to prevent disease. The oldest known medical text is the Eber's papyrus, which dates around 1550 BC and lists medicinal soil and moldy bread as treatments.[7] It has also recentlyproved that methicillin-resistant Staphylococcus aureus may be eliminated usingan Anglo-Saxon recipe from a thousand years ago,, or MRSA.[8] Nonetheless, Paul Ehrlich is generally credited with creating anti-infective medications and the fundamental idea of chemotherapy. He created the synthetic arsenic-based pro-drugs salvarsan (salvation arsenic) and neo-salvarsan about a century ago to treat Treponema pallidum, the syphilis-causing agent.[9] Inspired by Ehrlich's work on dyes that particularly marked bacterial cells, this was one of the first systematic screens for drug discovery employing a library of synthetic chemicals. Gerhard Domagk[10], a bacteriologist at Bayer, discovered the sulfonamide prodrug Prontosil, which replaced salvarsan.

He utilized the drugto keep his daughter's arm from being amputated. Domagk and others were essentially continuing Paul Ehrlich's work because the sulfa medications were based on dyes that were used to selectively highlight bacterial cells. The discovery of penicillin, which Alexander Fleming saw on a contaminated Petri dish in 1928, mainly replaced sulfonamides, which were the first really effective, broad spectrum antimicrobials in clinical usage and are still in use today.[11] Penicillin has subsequently purifie in Oxford researchers orman Ernst Chain, Howard Florey, Norman Heatley, and others who played a keyplayed a key role in the creation of the medication penicillin.[12] The beta-lactam structure of penicillin was figured out by Dorothy Hodgkin in 1945.[13] Settling the well-known argument between a number of prominent chemists, such like Robert Robinson, who favored a thiazolidine-oxazolone structure, and Abrahams, Chains, and Woodward, who believed it to be a beta-lactam.[14] This was an important finding since it allowed for the development of semi-synthetic derivatives that get around penicillin resistance.

Use of antibiotics

Numerous fields, including human health, animal husbandry, aquaculture, and agriculture.[15]

These drugs decrease crop loss from bacterial diseases by treating bacterial infections in people, animals, and crops.[16]

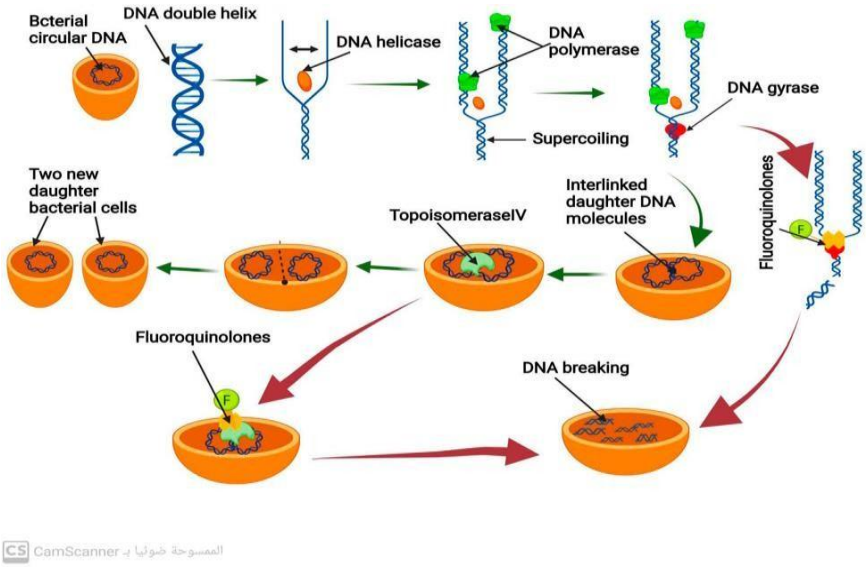
Antimicrobial agents are used to treat fish diseases in aquaculture. Antibiotics are administered to fish by adding them to specially prepared feed, and the majority of the time, the fish release the antibiotics into the environment.[17]

Mechanism of action of antibiotic

Scientists categorize antibiotics based on their chemical structure and mechanism of action because not all of them have the same precise mechanism of action.[18] The follwinjg mechanism, of action.

Antibiotics prevent the replication of DNA

Bacteria use binary Cell division known as fission produces two daughter cells. However, bacteria must make precise copies of their circular DNA before that can occur. The process by which DNA is duplicated is called DNA replication.[19] DNApolymerase and DNAhelicase activity ocauses the accumulation of positive DNA helical twists. DNA replication is inhibited by these positive helical twists. if they are not removed.Topoisomerase II is another name for the DNA gyrase enzyme., removes the positive superhelical twists so that DNA replication can proceed.[20] The 2A and 2B subunits make up DNA gyrase, an essential bacterial enzyme. Additionally, this enzyme is necessary for the start of DNA replication and the transcription of many genes. After being created, the two new daughter DNA molecules progressively unite and form a connection. The bacterial cell is divided into two new daughter bacterial cells by the enzyme topoisomerase IV, which is related to DNA gyrase and permits the separation of the two linked DNA molecules.[21]



Antibiotic prevent the protein synthesis

The process of protein biosynthesis begins with the DNA molecule's unwinding and separation at the place that codes for the necessary protein synthesis. The transcription process, which produces mRNA, is supported by a single strand of DNA. When finished, the mRNA strand binds to a ribosome and separates from the DNA template.The bacterial ribosome is composed of the 50 s and 30 s ribosomal subunits. The synthesis of the polypeptide chain begins once these two subunits link along the mRNA strand. The ribosome continues to add amino acids to the lengthening polypeptide chain until it receives a signal along the mRNA to stop. The entire chain of polypeptides is produced at this point.[22] Cell wall production is inhibited by antibiotics.While bacteria only some outer layer is present, the majority are made up of a cell membrane encased in a cell wall. Two functions of the bacterial cell wall are to maintain the bacteria's characteristic form and prevent them from rupturing when fluid is introduced into the cell by osmosis.[23] The most important component of the cell wall is the peptidoglycan. Peptidoglycan is a polymer made up of N-acetyl muramic acid (NAM) and N-acetyl glucosamine (NAG), which alternate and are joined by chains of amino acids.[24] The process of peptidoglycan production involves multiple phases and culminates in the development of bacterial cell walls. N-acetyl muramic acid and (NAG)N-acetyl glucosamine combine by precursor is form to peptidoglycan. After passing across the membrane, this peptidoglycan precursor is given to the periplasmic cell wall acceptors. The peptidoglycan precursors undergo significant cross-linking in the periplasm after binding to cell wall receptors.[25] The twise primary this enzymes involved in bacteria for cross-linking are trans peptidase as wellas carboxy peptidase. Eventually, several cross- linked peptidoglycan layers form a cell wallultimately arises from several cross-linked peptidoglycan layers[26] Because they may have more peptidoglycan layers, generally gram positive bacteria contain a thicker cell wall than gram-negative bacteria.[26]

Antibiotic resistance development

According to Dr. Tedros Adhanom Ghebreyesus, CEO of the World Health Organization (WHO), the global antibiotic resistance epidemic poses a major danger to a century of healthcare progress and the achievement of sustainable development goals.[27] Current projections indicate that nearly all bacteria will be resistant to the majority of antibiotics used in medicine within 25 years.[28] Additionally, experts estimate that by the middle of the twenty- first century, the number of fatalities from antimicrobial resistance could increase from the present annual total of over 700,000 to 10 million.[29]

Antibiotic Resistance mechanism

Bacteria prevent antibiotics from accumulating in their cells. By preventing medications from entering bacterial cells

The outer membrane of gram-negative bacteria has porin channels.[30] As gatekeepers, these channels restrict the entry of specific antibiotics, such as quinolones and B-lactams, into the bacterial cell. Consequently, a decrease in bacterial porins may prevent these antibiotics from entering the cell, increasing drug resistance.[31]

A. Speeding up the removal of antibiotics from bacterial cells

The cytoplasmic membrane of bacteria contains efflux pumps, which are essential for preserving the solute balance inside bacterial cells. However, These pumps also contribute to antibiotic resistance by eliminating drugs from bacterial cells before they can reach their intended targets.[31] Interestingly, it has been discovered that efflux systems impart resistance[32] to every class of antibiotic, with the exception of polymyxin.[33] Gaining more knowledge about the mechanics underpinning efflux systems could lead to the development of fresh approaches to the fight against antibiotic resistance.

B. Bacteria alter the antibiotic's target molecule

Since antibiotics are made to target particular molecules, even the smallest change can stop them from binding, which can result in the development of antibiotic resistance.[34]

a. alterations to the 30s or 50s ribosomal subunits

By altering their ribosomal 30S or 50S subunits, bacteria can become resistant to medications that interfere with protein synthesis.[35] This type of resistance is known to occur with antibiotics such aminoglycosides, tetracycline, macrolides, chloramphenicol, lincosamides, and streptogramin.[36]

b.Penicillin-binding protein (PBP) alterations

Enzymes known as transpeptidases, or penicillin-binding proteins (PBPs), are involved in the development of bacterial cell walls. —are essential for cross-linking peptidoglycan precursors. Since β-lactam antibiotics primarily target these enzymes, any modifications to their structure or activity may result in bacterial resistance to these medications.[37]

c. Alterations in the enzymes topoisomerase and DNA gyrase

DNA replication involves the enzymes topoisomerase and DNA gyrase.[38] Since quinolone antibiotics specifically target these two enzymes, modifications to their structure may result in bacterial resistance to quinolones.[39]

C. By using enzymes, bacteria render antibiotics inactive

Three essential enzymes are in charge of inactivating antibiotics. The following are examples of these enzymes

a. Enzymes called beta-lactamases

Every B-lactam antibiotic that has an amide and ester bond can be broken down by these bacterially generated enzymes. As a result, bacteria that are able to manufacture beta-lactamase enzymes become resistant to beta-lactamantibiotics.[40]

b.Enzymes that alter aminoglycosides (AGES)

Antibiotic resistance is known to be significantly influenced by enzymes. In particular, it has been discovered that some aminoglycoside-modifying enzymes (AMEs), stop aminoglycoside antibiotics from adhering to their ribosomal target.[41] Numerous bacterial strains, suchas S. aureus, S. pneumoniae, and E. faecalis, have these enzymes. These enzymes help to confer resistance to aminoglycosides and fluoroquinolones in addition to their function in inhibiting attach antibiotic.[42] Because it seriously impairs the ability of these antibiotics to effectively treat bacterial infections, the existence One of the main concerns in the study of antibiotic resistance is the presence of AMEs in bacterial strains. Enzymes of chloramphenicol-acetyl-transferases.

By acetylating the hydroxyl group of the antibiotic chloramphenicol, enzymes called chloramphenicol-acetyltransferases change the antibiotic and make it incapable of binding to its ribosomal target. Chloramphenicol antibiotics are therefore ineffective against bacteria that have the chloramphenicol-acetyltransferase enzyme.[43]

Bacterial resistance to antibiotics

Microorganisms are deemed resistant when they can grow or live at concentrations of antibiotics that normally prevents or destroys other members of the same species.[44] The words "susceptible" and "resistant" are frequently employed in clinical practice to characterize the possibility of an antibiotic therapy being successful.[45] When a patient cannot reach the dosage of antibacterial required to kill or inhibit the bacteria, resistance is more likely to develop.[46]

Antibiotic resistance can develop in microorganisms either naturally or as a result of exposure.[47]

Mutation of gene or the directlyresistance genes are transfer by two ways that resistance might evolve.[48]

Different resistant bacteria can spread and perhaps cause diseases in different environments because they can migrate in different ways. There are a few typical ways that resistant bacteria might spread, though the precise modes of movement may differ based on the bacterium and the surroundings. For instance:Person-to-person transmission: Through intimate contact, resistant bacteria can spread straight from one individual to another. Physical contact with an infected person, such as touching or shaking hands, or respiratory droplets from an infectedperson's cough or sneeze can cause this.[49]

Factors influencing antibiotic resistance

Underuse, overuse, or inappropriate antibiotics are used accelerates by emergence resitance of antibiotic.[50] Antibiotic usage in agriculture, drug promotion, prescribing physicians, inappropriate use of antibiotics by prescribers in human medicine, low-quality antibiotics, inadequate surveillance, and susceptibility testing are some of the factors contributing to the indiscriminate use of antibiotics, which encourages antibiotic resistance. Doctors and prescribers may be greatly swayed by patient demand even when they are aware of the patient's condition, which can lead to antibiotic and antimicrobial resistance.[51]

Patients may simply buy some of the drug, forget to take their prescriptions, or stop their therapy once they start feeling better. In these situations, more engagement between the doctor and the patient is frequently required to guarantee appropriate treatment compliance. Antibiotics are also easily obtained at pharmacies without a prescription, which encourages individuals to abuse them.[52]

The discovery of novel antibiotics

Teixobactin, a novel antibiotic that was discovered in 2015, showed bactericidal action against Clostridium difficile, Bacillus anthracis, and S. aureus. Researchers wrote an The paper "A Deep Learning Approach to Antibiotic Discovery"that was published in Cell on February 20, 2020. They found a novel antibiotic named halicin using artificial intelligence, and it demonstrated bactericidal effectiveness against a large number or range of resistant andbacteria is harmful.[53]

CONCLUSION

Numerous topics pertaining in antibiotics and there modes of action, Athe issue of antibacterial agent resistance, and remedies of their potential to counteract resistance have been covered this review article. Although antibiotics are used in many different industries, their usage is still debatable because of resistance problems. Antibiotics destroy or stop the growth of bacteria through four main ways.Nevertheless, bacteria have developed defenses against antibiotics, which reduces the medications' potency. We talked about a number of intriguing alternative strategies, such as the development of novel antibiotics, the application in adjuvants antibiotics basis on nanoparticles, botanics, and phages in light of limit effectiveness conventional resistancedue the antibacterial agent. Despite the difficulty of creating new antibacterial agent, and resistance challenge may be addressed by combining alternative approaches including phage therapy, adjuvants, botanicals, and nanoantibiotics.

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