EMERGENCE OF ANTIBACTERIAL RESISTANCE: NANOPARTCELS A NOVEL APPROACH TO COMBAT THIS CRISIS

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I. ANTIBIOTICS: BENEFITS AND CRISIS

Antibiotics made long lasting impact on medicine as being one of the most important discoveries of 20th era. They have played a pivotal role in combating bacterial infections and have saved countless lives, making a substantial positive impact on society. But, rise of drug-resistant pathogens is a major concern, and the major fear of inefficient treatment of infections has been an eminent concern from the beginning of the 21st century [1]. It facilitated advancements in various medical practices, including the successful outcomes of surgical procedures, the low use of immune suppressant drugs, and the enhanced utility of antimicrobial drugs for preventive steps and to control infectious complications. However, developing resistance against antimicrobials poses a major challenge to health care settings globally [2]. AMR is a natural consequence of evolution because all creatures undergo genomic alterations to evade deadly threats. Bacterial pathogens continuously enhanced their resistance mechanisms as frequently as antibacterial drugs were targeted at them. WHO reported (2019), 700,000 patients died due to the lack of efficient treatment available for drug

resistant microbial infections. It is estimated that this number will go as high as 20 million by 2050, with a $2.9 trillion economic burden [3]. Although in-depth research and development of new antibiotics costs a lot, with the drawback of a low investment return, apart from this very rapid mutation that led to AMR with limited therapeutics [4]. Although the situation appears dire, several new technologies hold the potential to bring about positive change. Scientific advancements in various fields hold the promise of helping to discover and develop novel antimicrobials. Synthetic techniques, along with inherent, responsible genomes and metagenomic research of pathogens, fauna, and marine invertebrates, intend to more quickly solve natural products and hasten the discovery of new antibiotics [5]. Various healing and precautionary measures, such as bacteriophages, are being explored as potential solutions [6]. Various other methods for battling bacterial infections comprise the use of homologous immunoglobulin [7] and vaccine [8]. These modern solutions combine with conventional techniques like synthetic organic and pharmacological chemistry, which continue to be key tools in the battle against AMR. To hold the post-antimicrobial age, progressive regulatory measures must be implemented.

II. WORLD BEFORE ANTIBIOTICS

Before the discovery of antibiotics, microbial infections were an area of limited research and poorly understood. In the past, the methods used to treat these contagious diseases and prevent their spread were ineffective, leading to frequent outbreaks and the loss of millions of lives [9]. As an example of the dire circumstances faced by people in the pre-antibiotic era, one can look to the outbreaks of the plague [10]. Nearly 100 million people lost their lives during the Justinian Plague, one of the pandemics occurred during the 14th century in Europe and hence termed "The Black Death" (66). Further, outbreaks of plague caused approximately 12 million deaths between 1895 and 1930. The first brick of antibiotic development was laid down by Antoine van Leeuwenhoek in 1676, when he developed the first microscope and saw the smallest living organism. This organism was termed **"animalcules"**. In 1871, Joseph Lister made a breakthrough discovery when he found *Penicillium glaucum*, a fungus that exhibits repressive properties against bacterial colonies. Later on, an extract of *P. glaucum* was used by him to treat his nurse's bacterial infection. This established the theory of infections caused by bacteria [11]. In the mid-19th century, Louis Pasteur and Robert Koch led independent research on bacteria. Louis Pasteur's research was focused on *Bacillus anthracis*, whereas *Mycobacterium tuberculosis* was the key bacteria for research led by Robert Koch. These two researchers established a theory of correlation between specific species of bacteria and disease, and the rest is history in the field of microbiology. These findings encourage the researchers to held more intense research for the discovery of novel antimicrobial compound for new age [12].

III. BEGINNING OF NEW ERA

Back in 1893, Bartolomeo Gosio, an Italian microbiologist, extracted mycophenolic acid from *Penicillium glaucum* which found to be effective against *Bacillus anthracis* [13]. Salvarsan (arsphenamine), the first arsenic-based antibiotic made in a lab, was found by Paul Ehrlich and his team in 1909. This innovative medicine was found to be effective in treating *Treponema pallidum* [14]. Its efficacy was improved in 1913 with the introduction of Neosalvarsan, a safer and more effective alternative to Salvarsan. These developments played a noteworthy part in advancing the area of antibiotic development [15]. Gerhard Domagk's

work on Prontosil revolutionized the field of antibiotic development and opened new doors for treating bacterial infections effectively [16]. Prontosil played a key role in combating bacterial infections by acting as a bacteriostatic agent. It accomplished this by preventing the dihydropteroate synthetase (DHPS) from entering the folic acid metabolism, thereby disrupting the bacteria's nucleic acid synthesis. This marked another significant milestone in the history of antibiotic research [17]. Studies reported that bacteria developed resistance to Prontosil due to mutations in the DHPS enzyme, rendering it less effective [18]. In 1928, Alexander Fleming, a Scottish bacteriologist, discovered that a *Penicillium notatum* fungus produced a substance that suppressed the population of *S. aureus*. Furthermore, this antibacterial molecule was isolated by him in 1929 and named "Penicillin". But H. W. Florey and E. B. Chain got a breakthrough in 1939 with their research that led to a better understanding of penicillin G. This was the first commercially available penicillin and was widely used to treat bacterial infections. They were able to purify the antibiotic and establish a method for large-scale production [19]. The introduction of penicillin as a therapeutic agent in 1945 marked a significant milestone in the history of antibiotic discovery [20]. In 1945, penicillin became available for use in treatment, marking a major breakthrough in the discovery of antibiotics. X-ray crystallographic analysis revealed the morphology of penicillin, making it the first naturally occurring β-lactam antibiotic [15]. Transpeptidases a key component of the cell which regulates the cross linking of the peptidoglycan, are the main target site by which cell wall synthesis inhibited causing cell death. Commercialization of Penicillin and other β-lactam anti-bacterial medications changes the fate of modern medicine and drastically decreases the fatality rates caused by the bacterial infections [21] [22]. In the 1960s, against various bacteria like *S. aureus, E. faecalis, H. influenzae*, *E. coli*, and *P. mirabilis*, chemically prepared methicillin, oxacillin, ampicillin, and carbenicillin exhibited impressive bactericidal potency. Nowadays, methicillin is not implemented for treating staphylococcal infections due to efficiently evolved resistance; however, ampicillin is still prescribed. MRSA is widely considered to be the first "superbug" [23].

IV. RISE OF ANTIBIOTICS AGE

Tyrothricin worked well against gram-positive bacteria, but it was too dangerous to be used in people. This made people keep looking for new and safer antibiotics, which led to the discovery of tetracyclines, macrolides, aminoglycosides, fluoroquinolones, and other groups of antibacterial drugs. Each of these antibiotics worked in a different way and only killed certain types of bacteria. This greatly increased the number of treatment options for microbial infections [24]. This discovery marked the discovery of several key antimicrobial agents, including actinomycin from *Streptomyces* and *S. fradiae* used for the isolation of neomycin, *Aspergillus clavatus* used for clavacin, and the famous fumigacin from *Aspergillus fumigatus* [25]. This time period saw significant advancements in the treatment of microbial infections and was also responsible for its widespread use in modern medicine. The discovery of antibiotics such as penicillin, streptomycin, neomycin, and many others revolutionized the way bacterial infections were treated and saved countless lives. Despite the rise of AMR strains and the decrease in the number of novel drugs being discovered, these older antibiotics remain essential components of the medical arsenal [26]. This vastly improved the treatment of bacterial illnesses and saved countless lives. During this time, it was considered that antibiotics were efficient against infections, and the pharmaceutical business strongly supported the development of new drugs. Despite this, the rapid increase of antibiotic resistance by bacteria poses a significant danger to the sustained usefulness of antibiotics, and

efforts are underway to find novel antibiotics and other treatment approaches [27]. This method contributed to the development of novel antibacterials, including, among others, tetracycline, macrolides, aminoglycosides, fluoroquinolones, and metronidazole. Inspite these efforts, the discovery of novel antibiotics has slowed in recent years due to problems in identifying new chemical entities, rising expenses of research and development, and the emergence of bacterial resistance mechanisms [23,28]. On the other hand, a very limited number of new drug groups have been derived since the discovery of penicillin, such as tetracyclines (1948), macrolides (1952), nitrofuran (1953), quinolones (1960), and oxazolidinones (1987) [29]. The upsurge of AMR strains established the need for novel techniques and compounds to combat them, including the development of new classes of antibiotics, alternative treatments such as phage therapy, and the implementation of prudent antibiotic use practices to slow the spread of resistance. WHO states that AMR is the 21st century's global threat to human health systems, food security, and growth [2]. However, due to the overuse of antimicrobial drugs and the dearth of investment in research, the advancement of novel drugs has been hindered in recent decades. Despite the discovery of over a thousand antimicrobial peptides, only one **"Colistin"** have been developed and approved for clinical use as antibiotics. This has resulted in the current situation where there are few new antibiotics in clinical trials and the medical community is facing an increasing threat of antibiotic resistance [30]. It is true that large pharmaceutical corporations are investing significantly less on identifying and isolation of novel antibacterials. Inadequate research coupled with an increase in antibiotic resistance has resulted in a significant drop in the number of new antibiotics entering the market. In the recent few decades, the situation has become increasingly alarming, and there has been a growing interest in discovering new sources of antibiotics and creating alternate strategies for battling bacterial illnesses. Smaller biotech companies and start-ups have been at the vanguard of this endeavor, but their limited resources represent a hurdle for the discovery and commercialization of novel antibiotics [31]. As per another report, only 2 out of 45 new antibacterial formulations proceeded to human trials [32]. The emergence of antibiotic resistance is the primary challenge facing the development and use of antibiotics. Despite initial recognition of antibiotic-resistant bacteria, a steady supply of new antibiotics enabled the selection of alternative treatments when resistance to a specific antibiotic emerged. This facilitated a straightforward shift in treatment strategy [33]. The limited development of antibiotics in recent decades has contributed to this catastrophe. Till date fluoroquinolones remains the only antibiotics commercialized in late 1980s, and after that no new class has been approved for human consumption since 1987. This lack of new antibiotics has resulted in a reduced pool of available treatment options when resistance to existing antibiotics arises [34,35]. Since the 1980s, the discovery and introduction of new antibiotic classes have been limited, and the few newly developed antibiotics in the pipeline are struggling to address the growing issue of antibiotic resistance [36]. Furthermore, companies are facing financial and regulatory obstacles for scientific research funding. However, experts predict that we may be entering again in a "pre-antibiotic era" due to the challenges of resistance and a lack of investment from pharmaceutical companies. Nevertheless, there has been a recent resurgence in funding for antibiotic research and innovation. Additionally, the use of phage therapy, probiotics, and prebiotics is also being explored as potential alternatives to antibiotics. There is also an increased interest in developing vaccines and immunotherapies to prevent bacterial infections. These alternative approaches have shown promise, but more research and development are needed to fully understand their potential and ensure their safety and efficacy [37]. To address the issue of antibiotic resistance, this includes exploring new methods for diagnosing and preventing

diseases as well as finding alternative treatments to antibiotics, such as phage therapy, probiotics, and anti-virulence strategies. Additionally, new approaches to drug discovery, such as computational methods, high-throughput screening, and synthetic biology, laid the groundwork for antibiotic development. The combination of these approaches is likely to deliver new answers to the growing problem of antibiotic resistance and help ensure a safe and effective supply of antibiotics for future generations [38]. In addition, whole genome sequencing (WGS) has proven essential in identifying new antibiotic targets and comprehending the causes of resistance, allowing for the development of new medicines and resistance-combating techniques. Other methods include the use of nanotechnology to improve the efficacy of antibiotics and the development of innovative antibacterial drugs that mimic the host's immune system. Moreover, there has been a resurgence in research into the development of vaccines to prevent infections as a substitute for antibiotics and reduce the overall burden of disease caused by bacteria. Overall, the landscape of antibiotic research and development is constantly evolving, and there is hope that these new approaches will lead to new and effective treatments to address the issue of antibiotic resistance [39]. Due to its potential to prevent bacterial infections by interfering with microbial cell-to-cell contact, the quorum-quenching (QQ) method is a relatively recent strategy that has received attention in the scientific community. This is yet another method by which drug-resistant strains emerge. While additional research is necessary to gain insight and develop effective preventive measures to combat this problem, it is now possible to identify the causes of the crisis [40]. Phage therapies are gaining fame as a potential alternative to antibiotics. This is due to their ability to target specific bacterial strains and their harmlessness to organisms and intestinal microbiota. This method of therapy has been found to be more effective. Although antibiotics is primarily consumed still phage treatment were in loop & gained renewed attention as a promising alternative to antibiotics in recent years. This is due to their effectiveness against bacterial infections as well as their safety profile, as they are harmless to host organisms and do not negatively impact gut flora, reducing the risk of opportunistic infections [41]. Genetic sequencing has accelerated clinical studies of biotechnology-derived humanized monoclonal antibodies. These advances have raised interest in using humanized monoclonal antibodies instead of antibiotics [42].

V. ANTIBIOTIC RESISTANCE REPORTS

Antibiotics are often referred to as "miracle drugs" for their effectiveness in combating bacterial infections. Their establishment and successive therapeutic utility are considered remarkable achievements in the history of medicine. For many years, antibiotics have been utilized not only for their medicinal properties but also as a preventive measure in various industries, such as animal husbandry and agriculture. AMR stands for "antimicrobial resistance," and it refers to the ability of pathogens to make drugs ineffective by resisting the effects of antibiotics that were previously effective against them, enabling the organisms to persist and multiply. As microorganisms evolve genomic modifications to counteract the cidal effects of antibiotics, AMR is an unavoidable spectacle [43]. The first instances of resistance were observed in gram-positive cocci shortly after the commercialization of penicillin for human consumption in 1941. In 1942, just a year after penicillin was introduced, penicillin-resistant *S. aureus* emerged. Similarly, in 1960, methicillin was approved for commercial use for treating infections in humans to combat *S. aureus*. However, the same year it was introduced, *S. aureus* developed resistance to methicillin. AMR has been a significant issue for many years, as bacteria can quickly develop resistance to antibiotics. It

was observed that about 705 of the microbial pathogens were resistant to at least one antibacterial drug. AMR stands as one of the major threats to the public. According to the report, nearly 2.8 million cases of AMR infections were detected in the United States alone, with over 35,000 deaths [44]. Particularly in India, one patient dies in every 9 minutes owing to AMR. In addition, it is anticipated that over 50,000 patients in India may perish from sepsis due to the inefficiency or evolved resistance to conventional antibiotics exhibited by pathogenic microorganisms [45]. The frequency of AMR in the European Union varied from 2015 to 2019. It was due to the etiological agent, and over consumption of selective antibiotics in various geographical locations. In USA alone 200K patients diagnosed with bacterial infection caused by AMR pathogens & approximately 20K died due to a lack of effective treatment [46]. Several reports highlight the globalization of AMR, with 500,000 cases of bacterial infections reported from 22 countries. *E. coli* contributes to the majority of the cases, followed by other bacterial strains, including *S. aureus, S. pneumonia,* and *K. pneumonia.* Ciprofloxacin initially showed impressive efficiency but later bacteria developed high level resistance against it. In 2019, 25 different nations submitted data to GLASS, reporting that MRSA is responsible for the majority of bloodstream infections (BSI), while 49 other countries reported *E. coli* as the major contributor to BSI. The incidence of MRSA was found to be 12.11%, and the frequency of third-generation cephalosporin-resistant *E. coli* was about 36% [47,48].

VI. REASONS BEHIND ANTIBIOTIC RESISTANCE

All microorganisms, including bacteria, evolve over time to achieve their objective of proliferating, surviving, and spreading as rapidly as possible, and adaptation remains one of the fundamental characteristics of microbes that develop in ways that ensure their survival. A chemical that restricts their growth, such as an antibiotic, may result in genetic alterations that render the bacteria resistant to the treatment and allow them to survive. Resistance among bacterial infections is a relatively natural occurrence. Concurrently, a number of additional variables also contribute to the development of resistance among certain bacterial infections. AMR is caused by bacterial changes, which can arise in a variety of ways, as described below:

1. **Genomic Transformation:** Point mutations during bacterial replication may replace one or more amino acids in a cell component like an enzyme, cell wall, or other cellular structure, a regulatory DNA segment, or chromosome alterations, creating novel resilient strains. The newly evolved guard may make antibiotics worthless, even if they were supposed to be effective previously [49].

2. **Genetic Material Transfer:** A once-susceptible strain may now be resistant to another species or genus. Plasmids and other mobile genetic components carry most antibiotic-resistant genes, which pass from bacteria to bacteria. Sensitive microorganisms may acquire drug-resistant genes. Drug-resistant bacteria are created by using new DNA. Environmental factors known as "selective pressure" permit organisms with unique mutations or newly evolved traits to survive and proliferate. Microbes are either killed when they are exposed to an antimicrobial agent or survive if they have resistance genes. These strains will proliferate, and freshly formed superbugs will quickly replace the existing microbial community as the dominant type [50].

3. **Inaccurate Diagnosis:** When diagnosing an illness, doctors can use weak or erroneous information and prescribe a wide-spectrum antibacterial drug or a certain narrow-spectrum antibiotics. These factors increase selection pressure and accelerate development of antibiotic resistance [51].

4. **Inappropriate Prescription of Antibiotics:** Antibiotics may be recommended if physicians are unclear whether bacteria or viruses are causing an illness, and this non-required consumption also contributes in the development of resistance [52].

5. **Self-Treatment:** Antibiotics are frequently administered without a doctor's prescription in Southeast Asia. These self-medications with antibiotics may result in inappropriate drug administration, putting patients in danger, concealing underlying symptoms, and fostering the emergence of resistant pathogens [53].

6. **Inadequate and Overuse of Antibiotics:** If a patient doesn't complete an antibiotic treatment, microorganisms may persist and become resistant. After realizing the hazards of overusing antibiotics, Alexander Fleming cautioned the public again in 1945. If you misuse antibiotics, bacteria may adapt and develop resistant [35].

7. **Poor Hospital Environment:** Every day, hundreds of patients, workers, and visitors enter hospitals with their own microbiome and bacteria on their skin, clothes, and organs. Bacteria may spread in hospitals without enough cleaning practices. Hence, AMR's rise is aided [54].

8. **Antibiotics in Agriculture as Growth Promoter:** All around the globe, antibiotics were routinely used as growth stimulants and nutritional supplements for animals. Similar to humans, misuse and overuse use of antibiotics in animals can lead to antibiotic-resistant bacteria as well. Humans are at risk of contracting antibiotic-resistant livestock pathogens that can be transferred through animal waste. Infections that are difficult to treat, persistent, and even fatal may arise [55].

9. **Availability of Few New Antibiotics:** Finding of new antimicrobials for targeting AMR bacteria has been hindered by a variety of obstacles, including technical concerns, a lack of understanding of bacterial physiology, financial or regulatory obstacles, and other factors. However, it is essential to note that new antibiotics have been created to treat antibiotic resistance, although it is feared that their use will hasten the development of resistance. As a result, physicians frequently save the newest antibiotics for life-threatening diseases while continuing to utilise proven-effective older drugs, which can increase the chance of bacterial resistance rendering these older agents ineffective [36].

VII. RESISTANCE MECHANISM AGAINST ANTIBIOTICS

Antibiotic resistance can be inherited or acquired through natural or induced means. The bactericidal action of antibiotics can be disintegrating cell construction, protein biosynthesis, nucleic acid synthesis, or metabolic pathways. Resistance can occur due to chromosomal DNA mutations or the acquisition of genetic material through translation, conjugation, or transposition. Antibiotic resistance can also result from drug target modification, inactivation,

efflux, and uptake limitation. Compared to GNB, GPC lack lipopolysaccharides in their outer membranes, which can reduce drug efflux and increase drug absorption [56].

1. **Antibiotics Inhibiting Cell Wall Synthesis:** Cross-linked peptidoglycan are presents in bacterial cell walls. β-lactam and glycopeptides prevent peptidoglycan synthesis, making cells more sensitive to osmotic pressure and autolysis. Bactericidal antibiotics impede cell wall formation. The approach works because animal cells lack peptidoglycan [57].

    Bacterial cell consist peptidoglycan, a mechanically supportive cell wall component. Gram-negative bacteria have one or two layers of peptidoglycan, whereas Gram-positive bacteria have 10–40 layers. β-lactam on transpeptidase or PBPs, which inhibit the formation of peptidoglycans. This disrupts terminal transpeptidation, causing bacteria to lyse. β-lactam antibiotics such as penicillin, cephalosporins, and carbapenems work by inhibiting bacterial cell wall synthesis, leading to bacterial death. β-lactam antibiotic resistance is caused by several mechanisms such as production of β-lactamases which hydrolyse the antibiotic's β-lactam ring, rendering it inert. Bacteria may manufacture penicillinases, cephalosporinases, and carbapenemases, which can make them resistant to some β-lactam antibiotics. Bacteria can alter the target site of β-lactam antibiotics, such as penicillin-binding proteins (PBPs), which cross-link the bacterial cell wall. This change can diminish the antibiotic's affinity for the target location, making it ineffective. Bacteria can lower the antibiotic's cell wall permeability to prevent its entrance. This can happen via altering porins, protein channels in the outer membrane that enable nutrients and other substances to pass. Bacteria can create efflux pumps, which aggressively pump antibiotics out of the cell to lower its concentration. [58]. Glycopeptides, such as vancomycin and teicoplanin, work by inhibiting bacterial cell wall synthesis, specifically by binding to the D-alanyl-D-alanine terminus of peptidoglycan precursor molecules, thereby preventing the cross-linking of peptidoglycan and inhibiting cell wall formation. Several mechanisms reported for resist glycopeptides including Bacteria can replace D-Ala-D-Ala in peptidoglycan precursor molecules with D-alanine-D-lactate or D-alanine-D-serine. This change lowers glycopeptide affinity for the peptidoglycan precursor, making the antibiotic ineffective. Bacteria can thicken their cell walls, making glycopeptides less accessible to the peptidoglycan layer and lowering their efficacy. Glycopeptides, like β-lactam antibiotics, may be pumped out of bacterial cells through efflux pumps. Some bacteria can acquire resistance genes like the VanA gene, which produces an alternative peptidoglycan precursor that does not bind to glycopeptides.[59].

2. **Antibiotics Inhibiting Protein Synthesis:** The 30S and 50S subunits of the bacterial 70S ribosome are called after their sedimentation coefficients in Svedberg units. The names come from the sedimentation coefficients of the 30S and 50S subunits, respectively. Antibiotics that limit protein synthesis in bacteria target the 30S or 50S ribosomal subunit, affecting protein synthesis and killing bacteria. Chloramphenicol, macrolides, and oxazolidinones bind to the 50S subunit, while aminoglycosides and tetracyclines attach to 30S [33]. Aminoglycosides, targets bacterial ribosome leads to protein synthesis inhibitions, leading to bacterial death. Several systems resist aminoglycosides. Bacteria can add chemical groups like acetyl, adenyl, or phosphoryl to the aminoglycoside molecule. This change decreases the antibiotic's ribosome affinity and efficacy. Bacteria can decrease the expression of porins or transporters needed to take in aminoglycosides.

Bacteria develop enzymes such aminoglycoside-modifying enzymes (AMEs) that chemically change the antibiotic molecule, inactivating it. Bacteria can alter the ribosome's structure, reducing the aminoglycoside's binding affinity [60]. Tetracyclines preventing the attachment of aminoacyl-tRNA to the ribosome. Various methods cause tetracycline resistance. Efflux pumps: Like other antibiotics, bacteria can create efflux pumps that actively pump tetracycline out of the cell, lowering its concentration. Ribosome protection proteins: Some bacteria create ribosome protection proteins that attach to the ribosome and prevent tetracycline from binding. Bacteria can create TET-enzymes that chemically alter the tetracycline molecule, rendering it inactive. Bacteria can reduce the expression of porins or transporters needed to take in tetracyclines. Bacteria can change the ribosome target location to reduce tetracycline binding.[61].

3. **Inhibitors of 50S Subunit:** Macrolides, such as erythromycin and azithromycin, work by binding to the bacterial ribosome and inhibiting bacterial protein synthesis. Several mechanisms cause macrolide resistance. Efflux pumps: Like other antibiotics, bacteria can create efflux pumps that actively pump macrolides out of the cell, lowering their concentration. Bacteria can change the ribosome target location to reduce macrolide binding. Enzymatic inactivation: Bacteria create enzymes like macrolide esterase or phosphotransferases that chemically alter the macrolide molecule, making it inactive. Mutation in ribosomal genes: Bacteria can modify ribosomal genes to change macrolide binding sites and diminish antibiotic affinity for the ribosome. Ribosome modification: Bacteria may methylate or acetylate ribosomal RNA, which reduces macrolide binding.[62]. Chloramphenicol act on microbial ribosomes causing inhibition of protein synthesis. Several systems resist chloramphenicol. Enzymatic inactivation: Bacteria can create enzymes such chloramphenicol acetyltransferases (CATs) or chloramphenicol phosphotransferases (CPTs) that chemically change the drug, making it inactive. Bacteria can reduce chloramphenicol absorption by decreasing porins or transporters. Like other antibiotics, bacteria can create efflux pumps that actively pump chloramphenicol out of the cell, lowering its concentration. Target site modification: Bacteria can change chloramphenicol's target site, such the ribosomal subunit, lowering its binding affinity. Ribosome modification: Bacteria can methylate or acetylate ribosomal RNA, which reduces chloramphenicol binding.[63]. Oxazolidinones bind to the bacterial ribosome to suppress protein synthesis. Various systems resist oxazolidinones. Bacteria can change the binding site of oxazolidinones, decreasing the antibiotic's affinity for the ribosome. they can alter the target ribosomal subunit site for oxazolidinones to reduce antibiotic binding affinity. Like other antibiotics, bacteria can create efflux pumps that actively pump oxazolidinones out of the cell, lowering their concentration. Bacteria may methylate or acetylate ribosomal RNA, which reduces oxazolidinone binding. Mutations and target site modification: Some bacteria gain resistance by ribosomal mutations and target site modification [64].

4. **Antibiotics Inhibiting Nucleic Acid Synthesis:** Some antibacterial drugs e.g., rifamycin and fluoroquinolones function by inhibiting RNA and DNA, respectively. Rifamycins block bacterial RNA polymerase, which is necessary for transcription. Several mechanisms cause rifamycin resistance. Mutations in the RNA polymerase gene: Bacteria can change the gene, changing the binding site of rifamycin and decreasing its affinity for the enzyme. Bacteria can alter the target site of rifamycin, such as the RNA polymerase, lowering its binding affinity. Like other antibiotics, bacteria can create efflux pumps that

actively pump rifamycin out of the cell, lowering its concentration. Enzymatic inactivation: Bacteria create enzymes that inactivate rifamycin. Mutations and target site modification: RNA polymerase mutations and target site modification can make bacteria resistant [65]. Ciprofloxacin and levofloxacin block bacterial DNA gyrase and topoisomerase IV, enzymes needed for DNA replication and repair. Fluoroquinolones are extensively used for their broad-spectrum activity and effectiveness against various bacterial illnesses, but resistance has become a public health issue. Target enzyme mutations cause resistance. Mutations in the DNA gyrase and topoisomerase IV genes can change fluoroquinolone binding sites and lower its affinity for target enzymes in bacteria. This reduces fluoroquinolone sensitivity and promotes resistance. Some bacteria limit fluoroquinolone uptake, preventing the antibiotic from entering the cell, in addition to target site alterations. Bacteria can also pump fluoroquinolones out of the cell via efflux pumps. Quinolones target Gram-positive topoisomerase IV. Gram-positive bacteria lack an outer membrane, making them more sensitive to topoisomerase IV medicines [66].

5. **Inhibition of Metabolic Pathways:** Sulfonamides and trimethoprim are synthetic antibiotics that act as anti-metabolites, or competitive inhibitors of bacterial metabolic enzymes. Specifically, they target different processes in the metabolism of folic acid. Sulfonamides actively bind and more efficiently binds with DHPS of PABA, which converts pteridine and PABA to dihydropteroic acid (DHP) in the folate biosynthesis pathway. DHP is then converted to tetrahydrofolate (THF), which is an essential cofactor in the synthesis of nucleic acids. Sulfonamides structurally resemble PABA and can bind to the active site of DHPS, thereby inhibiting the enzyme's activity. This leads to a decrease in THF production and ultimately, a decrease in the synthesis of nucleic acids, which is necessary for bacterial growth and proliferation.

   However, it should be noted that THF does not produce purines and dTMP directly. Rather, it acts as a cofactor in the synthesis of these molecules. Purines and dTMP are synthesized from IMP and dUMP, respectively, which are produced in the presence of THF. Therefore, the inhibition of THF synthesis by sulfonamides indirectly leads to the inhibition of purine and dTMP synthesis, which limits bacterial growth [67]. Trimethoprim inhibits the enzyme dihydrofolate reductase (DHFR), which is involved in the folate biosynthesis pathway. DHFR converts dihydrofolate (DHF) to tetrahydrofolate (THF), which is a cofactor necessary for the synthesis of nucleic acids and other important biomolecules in bacteria. By inhibiting DHFR, trimethoprim reduces the amount of THF available for bacterial metabolism, leading to impaired nucleic acid and protein synthesis and ultimately, bacterial death. (161). Inhibiting THF production kills bacteria. Sulfamethoxazole & trimethoprim may impede the stage before bacterial protein synthesis. Sulfamethoxazole and trimethoprim block two bacterial protein and nucleic acid synthesis steps. Trimethoprim alone is bacteriostatic, but with sulfamethoxazole, it is bactericidal [68].

6. **Limiting Drug Uptake:** GNB have a lipopolysaccharide (LPS) coating on their outer membrane, making them less susceptible to drugs. This natural barrier prevents glycopeptide medicines like vancomycin from penetrating the outer membrane and killing gram-negative bacteria. Polar molecules cannot penetrate *enterococci* cell walls due to downregulation of porin channels or replacement with non-selective channels, which

impart aminoglycoside resistance. Recent studies suggest that porin expression alterations in *Acinetobacter spp., Pseudomonas spp.,* and *Enterobacterales* may have caused carbapenem resistance. In *Enterobacterales*, carbapenem resistance develops if carbapenemase enzymes are absent, porin production is lowered by mutations, or mutant porin alleles are present. Biofilms help microorganisms colonize. Biofilm matrix polysaccharides, proteins, and DNA protect the bacteria against antimicrobial medicines [69].

7. **Drug Efflux:** Bacterial efflux pumps remove numerous antibiotics from Gram-negative bacteria, making them resistant. The ABC, SMR, MATE, RND, and MFS efflux pump families are classified by structure and energy source. RND pumps transfer substrates across the cytoplasmic membrane. Tet efflux pumps eject tetracyclines through proton exchange. Tetracyclines can be extruded by *P. aeruginosa* with MexAB-OprM and *Enterobacterales* with AcrAB-TolC. Clinically important efflux pathway characteristics include macrolide resistance. The best-studied efflux pumps expel macrolide drugs [70].

8. **Drug Inactivation:** Bacteria degrade or chemically change antibiotics to inactivate them. Bacteria may produce enzymes that link chemicals to drugs. Antibiotics can't reach germs. Chemically inactivating medications containing phosphoryl, acetyl, and adenyl groups works well. Aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones are acetylated most often. Adenylation and phosphorylation may target aminoglycosides. AMEs inactivate aminoglycosides by covalently altering hydroxyl or amino groups. Drug modification-based resistance [60]. Penicillin and cephalosporins are the most common antibacterials. A four-sided β-lactam loop characterizes this pharmacological class. The main resistance mechanism is broken by β-lactamases, which break the β-lactam loop. β-lactamases hydrolyze beta-lactam ring formation, preventing PBP binding [22].

Antibiotics are drugs that are used to treat bacterial infections by targeting specific cellular processes of bacteria. However, with the overuse and misuse of antibiotics, bacteria have developed various mechanisms to resist the effects of these drugs. One such mechanism is drug target modification, which involves altering the cellular target of the antibiotic, rendering it ineffective. Bacteria can modify their drug targets in a variety of ways. One common method is through mutations in the genes that encode for the target proteins. For example, bacteria can acquire mutations in the gene that encodes for the bacterial ribosome, which is the target of many antibiotics such as macrolides, tetracyclines, and aminoglycosides. These mutations can result in changes to the structure or function of the ribosome, which can reduce the binding affinity of the antibiotic and make it less effective. Another way that bacteria can modify their drug targets is through the acquisition of new genes that encode for modified or altered target proteins. For example, bacteria can acquire plasmids that carry genes encoding for beta-lactamases, which are enzymes that hydrolyze the beta-lactam ring of antibiotics such as penicillin and cephalosporins. These beta-lactamase enzymes can modify the target proteins, rendering the antibiotics ineffective. Bacteria can also modify their drug targets by altering the expression of the genes that encode for these targets. Drug target modification is a significant mechanism of antibiotic resistance and can occur rapidly, leading to the emergence of resistant bacterial strains. Additionally, bacteria can utilize multiple

mechanisms of resistance, including drug target modification, making it even more challenging to treat infections caused by these resistant strains.

To overcome antibiotic resistance due to drug target modification, researchers are exploring alternative strategies that target bacterial processes that are less prone to resistance. For example, researchers are developing new antibiotics that target alternative bacterial processes, such as bacterial cell wall synthesis or DNA replication. Additionally, researchers are exploring combination therapies, where multiple antibiotics are used simultaneously, targeting different bacterial processes to minimize the development of resistance [22].

VIII. NANOMEDICINE AGAINST AMR

Nanomedicine-based pharmaceuticals have improved biodistribution, targeting, and absorption. Nanometer-sized particles load hydrophilic and lipophilic drugs more efficiently, increasing antibacterial activity. Nanosystems can traverse the reticuloendothelial system, making antibiotic absorption more efficient. Nanosystems interact with proteins, tissues, and tissue components through their surface charge and zeta potential, affecting cellular biodistribution and absorption. Anionic host cells like macrophages prefer positively charged nanosystems. Nanoparticles may alter the structure of bacterial cells, killing them. Nanophotothermal therapy also kills bacteria with inorganic nanoparticles like AuNPs [71].

Antibacterial Nanoparticles

Nanoparticles with antibacterial properties, typically less than 100 nanometers in size, are used to effectively target and eliminate harmful microorganisms such as bacteria, viruses, and fungi. These particles possess unique physical and chemical attributes. They can be composed of a range of materials, including metals like silver, gold, and copper, polymers, or ceramics. Silver, due to its high potency and low toxicity to mammalian cells, is the most commonly used material for these particles. The mode of action of antibacterial nanoparticles differs based on the material and size. Some release toxic ions that interfere with the metabolic processes of microorganisms, leading to their death, while others create physical barriers on surfaces, hindering the growth and spread of microorganisms [72].

Textiles, medical and dental equipment, wound dressings, and food packaging employ antibacterial nanoparticles. Its medical use may reduce hospital-acquired infections and increase antibiotic efficacy. Bacterial infections cause many chronic diseases and deaths. Antibiotics cure bacterial illnesses and have several benefits, including a low cost, a high success rate, a quick response, and flexible administration (such as oral, topical, intravenous, or intramuscular injection). Penicillin, Sulphonamides, erythromycin, methicillin, and ampicillin were created during the 1930s and 1970s. Due to the enormous expense of screening tests, regulatory restrictions, and clinical trials, the development of novel antibiotics has almost halted [73,74]. Methicillin-resistant *S. aureus*, a deadly infection, is tough to treat. MRSA is found in 5% of US hospitalized patients' skin or nasal cavities, according to the CDC. MRSA may cause pneumonia, sepsis, bloodstream infections, skin infections, and even death. Nanostructured surfaces with metallic nanoparticles may inhibit *Staphylococcus* biofilm on medical equipment [75,76].

Metal ions and nanoparticles have been researched as alternatives to antibiotics for treating bacterial infections. Metal nanoparticles affect a wide range of bacterial strains and microorganism macromolecules. Electrostatics attract metal nanoparticles to the cell wall. Second, connected nanoparticles produce ions that break the cell wall and allow membrane internalization. These ions may impact protein-synthesizing enzymes, proteins, and ribosomes within the cell. They stop DNA replication. Redox-active metal ions overproduce oxidative stress, genetic material alteration, free radical generation, and lipid peroxides, which cause cell death, metabolic failure, and metal ion buildup [77].

Designing and synthesizing antibacterial metal nanoparticles requires consideration of dimensions, conformation, configuration, and zeta potential. Ultra NPs of size ranging 0.5–3 nm, & tiny nanoparticles with size of 3–50 nm efficiently kills bacteria better than bigger nanoparticles. Surfactants, ligands, and coatings may change nanoparticle shape and surface charge, and biological applications favor water-soluble, colloidal-stable, and mildly charged nanoparticles. Ag, Cu, Fe, ZnO, Au, TiO$_2$, Al, CeO$_2$, and tungsten carbide (WC) have antibacterial qualities. Metal nanoparticle solutions may coat or spray surfaces to make them bioactive or antiseptic. Self-cleaning glass, air purifiers, clothes, medical equipment, cleaning chemicals, food packaging, and antibacterial creams, lotions, and ointments may use nanoparticles to control germs [78].

It is worth noting that although antibacterial nanoparticles have demonstrated encouraging results in managing bacterial infections, they also have the potential to have adverse effects on both the environment and human health. Some studies have raised concerns regarding the accumulation of nanoparticles in the environment and their potential to harm non-target organisms. Moreover, the rise of antibiotic-resistant bacteria is an increasing concern, and the excessive use of antibacterial nanoparticles may contribute to this issue. Overall, antibacterial nanoparticles have significant potential for controlling bacterial infections; however, further research is necessary to comprehensively understand their safety and long-term consequences.

IX. INTERACTIONS OF NANOMATERIALS WITH LIVING ORGANISMS

Because of recent developments in nanotechnology, researchers may now tailor NMs to meet a wide range of functional needs. The Nano Database now records a total of 4494 nanomaterials in a variety of forms that are commercially accessible for use in a wide range of industrial and consumer applications. Yet, NMs have the potential to become environmental contaminants and interact with biological creatures due to their rising usage and disposal. It is possible for humans to be exposed to NMs during either the production or consumption of these goods, whether it be through the skin (from using sunscreens or other personal care products containing NMs), the lungs (from breathing in NMs released into the atmosphere), or the stomach (from ingesting NMs present in water or food). When employed as pharmaceuticals, NMs will have intense interactions with humans, the nature of which may vary with the specific drug. NMs may be swallowed, breathed in, injected, or absorbed via the skin and then taken up by the cells of the targeted tissues by one of many endocytosis routes. In the following paragraphs, we will discuss how the entrance point of NMs influences their biodistribution and toxicity [79].

X. TOXICITY TRAITS OF NANOMATERIAL

1. **In Vitro Toxicity of Nanomaterial:** The possible risks caused by NMs may be understood by in vitro testing, which also offers in-depth, cellular-level information. These checks are simple to conduct and let scientists compare several factors in a single study. Although it is true that in vitro studies may shed light on how NMs act in vivo, this link is not always reliable. Several studies have shown that there seems to be a difference between in vitro and in vivo results. Inconsistencies like this may be traced back to variations in experimental design and the complexity of the biological systems being studied. Thus, more systematic data generation is required for data reconciliation. NMs have been shown to have varying effects on live organisms in in vitro experiments. When interacting with biological organisms, NMs may have harmful consequences both inside and outside the cell. One of the main causes of NM toxicity is oxidative stress. Depending on their optical or physicochemical features, NMs may generate ROS via a variety of methods. Highly reactive and non-specific, ROS may change the function of a wide variety of biomolecules via interactions with these molecules. Damage to lipids, proteins, and DNA, as well as inflammation and activation of the adaptive immune system and the beginning of apoptotic and necrotic pathways, may all result from oxidative stress. Because of their existence, certain NMs may cause membrane damage and affect the fluidity of cell membranes. When the NMs have a high positive zeta potential, they become physically and chemically attracted to the cell membrane. Damage to the outer membrane lipid, increased cell permeability, and NM entrance into the cytoplasm may all arise from this interaction. Damage to the cytoskeleton, brought on by NM exposure, may alter cell shape, activity, and organelle function. Many factors, including reactive oxygen species (ROS) induction, physical contact, and intracellular energy imbalances, have been linked to this phenomenon. Two-dimensional cell cultures and fluorescence-based tests, the current gold standard for gauging nanotoxicity, have low sensitivity and poor concordance with in vivo research. Nevertheless, technological advancements have allowed for the creation of 3D cell cultures and sophisticated cell imaging methods, including electron microscopy and holotomography. Real-time analysis of the intracellular distribution of NMs and their consequences is made possible by holotomographic imaging, which contributes to a better understanding of NMs in cells [80,81].

2. **In Vivo Toxicity of Nanomaterials:** Many studies have investigated the toxicity of NMs in a wide range of species, from bacteria to humans. Yet as the complexity of the organism rises, so does the difficulty of assessing its toxicity. In vivo research examines the presence and toxicity of NMs in animal models with the hope of drawing parallels to their effects on humans. The zebrafish (Danio rerio) is one of several animal models that may be used for this purpose; it is particularly well-suited because of its quick growth and high degree of resemblance to humans. To learn more about how NMs affect certain organs, scientists often turn to animal models. Several routes of administration, such as ingestion, inhalation, ocular contact, and skin absorption, provide different results when it comes to the effects of NMs on a living thing. The liver, spleen, bladder, kidney, lungs, heart, and testes are just a few of the organs that the NMs may reach through the circulatory system. As NM accumulates in certain areas, inflammation often develops. NMs may also disrupt digestion and food absorption, leading to nutritional deficits. NM contact may cause harm to the GI tract by particle absorption, oxidative stress, and

hyperplasia. When NMs are ingested orally, they are mostly eliminated through the feces after being distributed to the liver, spleen, kidneys, and heart. Depending on the severity and duration of the exposure, NMs may cause skin irritation, inflammation, sensitivity, and premature aging. Although some research indicates that NMs cannot pass through the skin's upper layers, others demonstrate that, depending on their size, NMs may pass past the hair follicles and reach the deeper layers. Only when the skin is destroyed or when specialized procedures are employed to affect the structure of the skin can translocation occur, enabling NMs to enter the circulatory system or other organs. The alveoli may be exposed to NMs after inhalation, which may lead to oxidative stress, inflammation, immune cell infiltration, and alveolar destruction. Respiratory disorders like pulmonary fibrosis, lung cancer, and emphysema have been linked to long-term exposure to NMs. The translocation of NMs to other organs like the brain, heart, liver, spleen, kidneys, and gastrointestinal system is influenced by factors like the proximity of alveolar cells to blood vessels and the absorption of NMs by immune cells. Urinary and intestinal excretion are the main routes of NM elimination. Exposure to NMs can lead to inflammation, oxidative stress, DNA damage, suppression of antioxidant mechanisms, and changes in the extracellular matrix of ocular cells. The size of particles plays a crucial role in their translocation, with only particles smaller than 5 nm able to cross the whole eye and enter the systemic circulation. Even though the CNS is not directly associated with NP exposure, NMs can cross the blood-brain barrier (BBB) through inhalation and affect the brain, leading to oxidative stress, DNA damage, release of proinflammatory cytokines, alterations in neurotransmitter synthesis and metabolism, malfunction of transmembrane protein complexes, and modification of intracellular calcium ion levels. Prenatal exposure to NMs has been linked to brain and cerebellar atrophy, reduced neuron density in the cerebral cortex, hippocampal pyramidal cell injury, and deficits in learning and memory. Since the immune system comes into contact with NMs through inhalation, ingestion, and skin contact, it plays an important role in the exposure of the body to NMs. Protection against NM harm falls on the shoulders of the immune system, and the NMs' protein corona plays a crucial part in this protection by defining the innate immune response and the removal of NMs. Nano-biological interactions in the respiratory, cutaneous, gastrointestinal, and circulatory systems are triggered by the presence of immune cells, which phagocytose NMs and destroy them. However, bio-persistent NMs may avoid destruction by immune cells, allowing them to spread through the circulatory system and spread to other organs. It is difficult to generalize these results owing to the uniqueness of many investigations; however, this biodistribution of NMs may cause systemic harm [82].

XI. THE FUTURE AND CHALLENGES OF NANOPARTICLES

Nanomaterials are widely used in ecosystems, but their potential toxicity and health effects remain unclear due to a lack of data. Standardized standards are needed to assess the riskiness of nanomaterials, categorizing them based on their composition, structure, chemical and biological interactions, exposure potential, and toxicity endpoints. However, obstacles such as lack of reference materials, divergent opinions on endpoints, interference in tests, and inconsistent batches are hindering progress. To reduce toxicity and make nanomaterials suitable for medical use, they should be developed with enhanced activity and biocompatible characteristics. Consistent methods for investigating interactions between nanomaterials and live creatures are needed to understand their harmful effects. In-vitro and in-vivo experiments

are needed to identify effective dosage and toxicity traits. Controls and standardized techniques are crucial for detecting and removing confounding variables. Despite the abundance of literature on nanomaterial toxicity, "omics" approaches, simple living models, and in silico research can help understand the potential hazards of nanomaterials.

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