



Innovations in the Treatment of Antibiotic-Resistant Bacterial Infections: From Drugs to Alternative Approaches

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الابتكارات في علاج الالتهابات البكتيرية المقاومة للمضادات الحيوية: من الأدوية إلى الأساليب البديلة

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Accepted:

1/9/2025

Published:

30/9/2025

ABSTRACT

Infections resulting from antibiotic-resistant bacteria (ARB) represent a major global health concern of our era. Alongside the development of novel antibiotics, the identification of antibiotic-resistant microorganisms and the exploration of alternatives to current medications present viable strategies to address antibiotic resistance. This analysis consolidates the most promising solutions for combating ARB that are currently in development. These strategies encompass: (a) the discovery of novel antibiotics through the modification of existing compounds; (b) the enhancement of the efficacy of current antibiotics via metabolic stimulation or the implementation of advanced delivery systems; and (c) the emergence of novel alternatives to traditional antibiotics includes bacteriophages and endolysins, anti-biofilm compounds, probiotics, nanomaterials, vaccines, and antibody-based therapies. Preclinical and clinical investigations indicate that these treatments possess significant potential against antibiotic-resistant microorganisms. Certain ARB items are anticipated to be commercially accessible in the imminent future.

Keywords: Antibiotics, Alternative Methods, and Resistant Bacteria



INTRODUCTION

The discovery of penicillin by Alexander Fleming in 1928 marked a pivotal turning point in the history of modern medicine, revolutionizing the fight against bacterial diseases, previously a leading cause of death worldwide. With the introduction of penicillin as the first effective antibiotic into clinical use, mortality rates from bacterial infections declined significantly, leading to the development of new generations of antibiotics. This achievement improved the quality of healthcare and reduced the burden of many serious infections [1].

Antibiotic resistance (AMR) is one of the major health challenges facing humanity today. Resistance arises primarily as a result of the excessive and inappropriate use of antibiotics in human medicine and agriculture, coupled with weak control and prescription systems in many countries[2]. In 2017, the World Health Organisation published a list of twelve bacteria classified as problematic due to their resistance to numerous widely available antibiotics. The encompassed bacteria include

Acinetobacter baumannii, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Enterococcus faecium*, *Staphylococcus aureus*, *Helicobacter pylori*, *Campylobacter spp.*, *Salmonella spp.*, *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Shigella spp.* (fluoroquinolone-resistant) [3].

Molecularly, bacteria develop several strategies to defend themselves against antibiotics, such as producing degradative enzymes (such as β -lactamases), modifying drug target sites, enhancing the extracellular release of antibiotics, and reducing cell wall permeability. These mechanisms are often transmitted via mobile genetic elements such as plasmids, and resistance mutates rapidly and affects several species of bacteria in different environments[4].

This resistance poses a threat that goes beyond traditional antibiotics. Simple diseases, such as urinary tract infections or wounds, become difficult and costly to treat. Advanced medical procedures, such as organ transplantation and chemotherapy, also rely on the effectiveness of effective antibiotics, while increased resistance can render these procedures ineffective. A multitude of scientists globally are currently concentrating on devising methods to address

antibiotic-resistant bacteria (ARB) to avert the potential unavailability of effective antibiotics in clinical settings in the future. This review examines the recent advancements in efforts to address the rise of antimicrobial-resistant bacteria (ARB) are documented in the literature, emphasizing commendable chemical, microbiological, and immunological procedures (Figure 1)[5]. This review aims to highlight the latest innovations in the treatment of antibiotic-resistant bacterial infections by reviewing developments in improved drugs, strategies to modify traditional antibiotics, and non-drug alternatives such as immunotherapies, bacteriophages, nanocomposites, and plant extracts, in addition to analyze the effectiveness of these new approaches and compare them with the current challenges facing modern medicine in combating multiresistant bacterial strains, with the goal of providing a comprehensive view of future trends in this vital field.

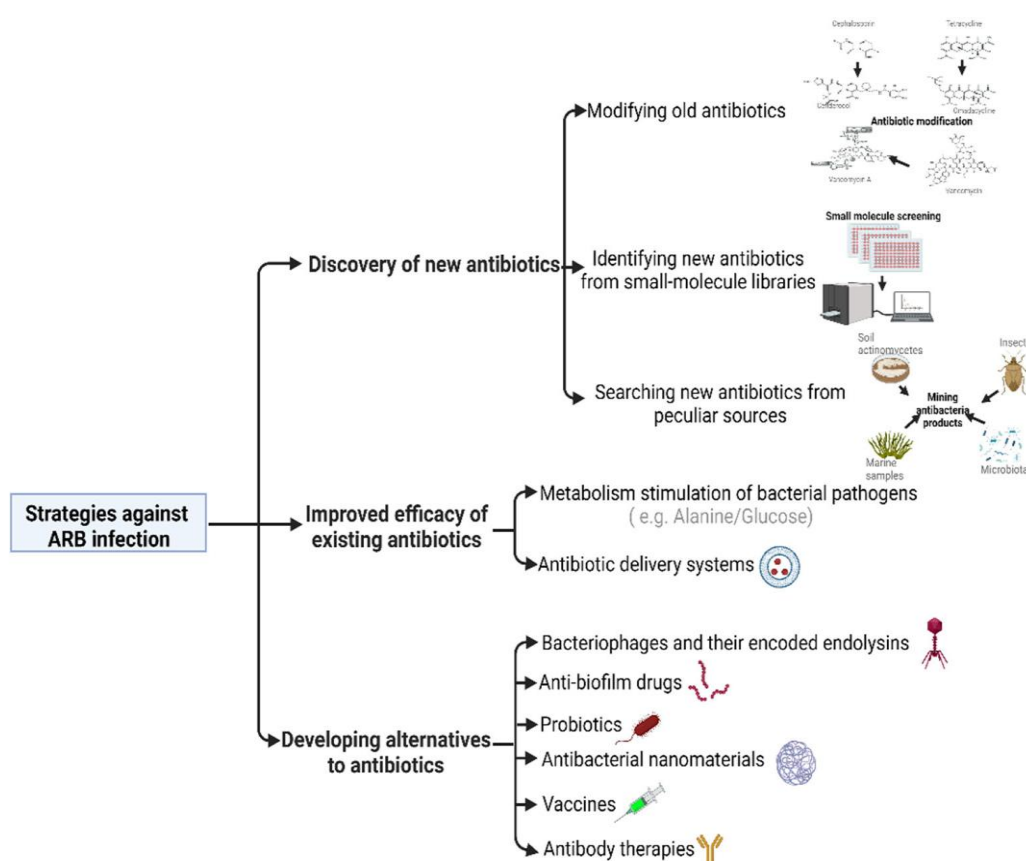


Figure 1. Strategies for combating antibiotic-resistant bacterial infections [5].



2. The Global Burden of Antibiotic Resistance on Public Health

The magnitude of antibiotic resistance is now widely recognized as one of the greatest challenges to public health worldwide. The World Health Organization (WHO) declared antimicrobial resistance (AMR) a top ten global public health threat in 2019. A comprehensive analysis published in *The Lancet* estimated that in 2019 alone, approximately 4.95 million deaths were associated with bacterial AMR, with 1.27 million of them directly attributable to resistant infections [6].

Geographically, the burden is unequally distributed. Sub-Saharan Africa and South Asia report some of the highest mortality rates due to resistant infections, often exacerbated by poor healthcare infrastructure, limited access to diagnostics, and inadequate surveillance systems [7]. In high-income countries, although robust antibiotic stewardship programs have been implemented, the problem persists due to factors such as hospital-acquired infections, multidrug-resistant organisms (MDROs), and an aging population with frequent antibiotic exposure[8].

The economic consequences of antibiotic resistance are equally alarming. The World Bank (2017) warned that if current trends continue, the global economy could experience a cumulative loss of \$100 trillion by 2050, primarily due to increased healthcare costs, loss of productivity, and reduced agricultural output. Moreover, the pressure on healthcare systems is growing, as resistant infections require more expensive and toxic alternative treatments, extended hospital stays, and intensive care resource[9].

3. THE MOST PROMISING SOLUTIONS FOR COMBATING ARB THAT ARE CURRENTLY IN DEVELOPMENT

3.1 Discovery of New Antibiotics

The majority of multinational pharmaceutical firms have reduced their investments in the research and development of novel antibiotics. Nonetheless, research teams in hospitals or academic institutions beyond the industry continue to contribute to the pipeline aimed at addressing ARB.

3.1.1 Modifying old antibiotics

Modifying old antibiotics is one of the most effective strategies for combating antibiotic resistance, especially given the slow and costly process of developing entirely new drug molecules. This approach relies on redesigning or improving the molecular structure of known antibiotics, with the goal of restoring their effectiveness or enhancing their pharmacological properties to overcome the resistance mechanisms developed by bacteria[8].

This strategy is based on the principle that many classic antibiotics, despite losing their effectiveness against some resistant strains, still possess potent and effective molecular cores. By chemically modifying these molecules, we can inactivate resistant bacterial enzymes, enhance drug permeability across the bacterial cell membrane, or reduce the bacteria's ability to excrete the antibiotic via efflux pumps[10]. Omadacycline, a semisynthetic derivative of tetracycline, possesses changes at the C-7 and C-9 positions of the tetracycline D-ring, allowing it to circumvent prevalent tetracycline resistance mechanisms, including as tetracycline-specific efflux pumps and

ribosome protection, which helps to overcome the resistance mechanisms that bacteria develop against it, FDA approved in 2018 for CAP and ABSSSI [11].

Vancomycin is extensively utilized to address infections caused by *E. faecium* or methicillin-resistant *S. aureus* (MRSA), although its efficacy has diminished due to the prevalence of vancomycin-resistant strains in hospitals and communities [12]. To address vancomycin resistance, the Boger laboratory at the Scripps Research Institute has dedicated over a decade to altering the fundamental structure of vancomycin, ultimately producing a series of synthetic analogues known as the maxamycins group (Figure 2), which exhibit significant bactericidal activity against vancomycin-resistant *E. faecium* (VRE) and *S. aureus* (VRSA) isolates [13]. This research group has devised a scalable atroposelective total synthesis method for vancomycin analogues that significantly decreases the number of steps needed and improves the overall yield, facilitating the production of amounts required for preclinical evaluation [14, 15].

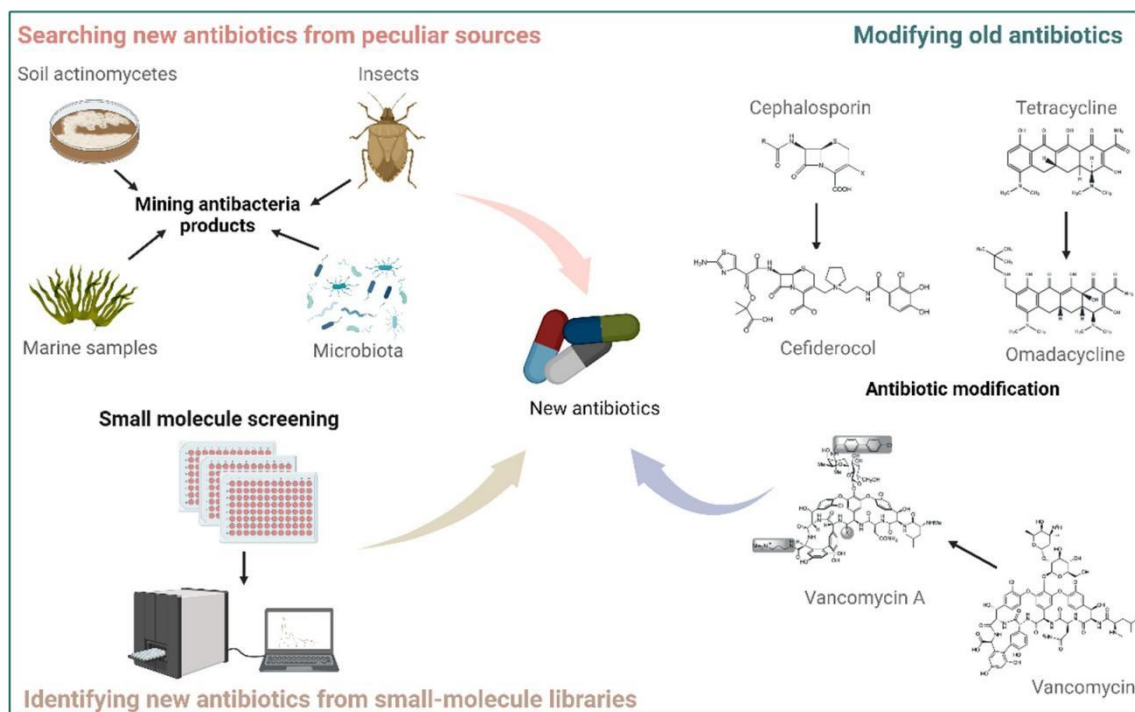


Figure 2. Strategies used to extract new antibiotics.



4. IMPROVED EFFICACY OF EXISTING ANTIBIOTICS

Improving the effectiveness of existing antibiotics is a crucial strategy to address the growing challenges associated with bacterial resistance to antibiotics, which threatens the effectiveness of many clinical treatments. Given the limited discovery of new antibiotics, interest has emerged in developing scientific and technical methods to enhance the effectiveness of currently available antibiotics, whether by improving their pharmacological properties or redirecting their use against resistant strains [2].

4.1 Metabolism Stimulation of Bacterial Pathogens

Stimulating metabolism in pathogenic bacteria is an emerging and unconventional strategy for combating bacterial infections, especially those resistant to antibiotics[16]. Unlike the traditional approach of directly inhibiting or killing bacteria, this strategy is based on the principle of stimulating certain metabolic pathways within the bacterial cell to make them more susceptible to antibiotics, or to trigger intrinsic mechanisms that lead to their death[17]. However, this concept is still largely experimental and has not yet reached clinical translation. It is primarily explored in laboratory and preclinical studies, where it shows promising potential but requires further validation in human applications.

Numerous studies have shown that modifying bacterial metabolism is a highly effective approach to enhancing the effectiveness of antibiotics[18]. To achieve this goal, two metabolic-based regulatory strategies are available: (1) enhancing metabolic pathways that increase bacterial susceptibility to antibiotics, and (2) inhibiting metabolic pathways that increase antibiotic resistance[19].

One prominent application of this concept is forcing bacteria out of metabolic dormancy, a state adopted by some strains, such as bacteria within biofilms, or bacteria "resting" within the host to evade the effects of antibiotics[20]. In this state, the metabolic rate is very low, reducing the effectiveness of most antibiotics, which require an active cell to be effective [21].

In addition, recent research has shown that enhancing certain metabolic pathways, such as the TCA cycle or NADH production, can increase the accumulation of free radicals (ROS) within the



cell, leading to damage to DNA and proteins, and ultimately leading to bacterial cell death[16]. Certain chemicals and nutrients, such as amino acids or simple sugars (glucose, mannitol), can be used to stimulate these pathways and enhance bacterial sensitivity to antibiotics[22]. In study [22] noted that a kanamycin-resistant strain of *Edwardsiella tarda* exhibited a deficiency in L-alanine and glucose relative to the wild-type strain. These metabolites significantly enhanced kanamycin absorption and toxicity via the stimulation of the TCA cycle and the augmentation of the proton-motive force (Figure 3). The increased intracellular concentration of kanamycin likely surpassed the resistance threshold established by spontaneous suppressor mutations. Comparable potentiation procedures were employed in other research, consistently concluding that ARB might be regulated by antibiotics in conjunction with diverse metabolites from glycolysis, the TCA cycle, and amino acid metabolism [23].

One practical application of this strategy has been tested in *Staphylococcus aureus* and *Escherichia coli*, where combining metabolic stimulants with traditional antibiotics such as ampicillin and gentamicin showed significant improvements in antibacterial efficacy, even against resistant strains. This was attributed to increased antibiotic flow into the cell due to the stimulated metabolic activity and increased energy consumption[24].



4.2. Antibiotic Delivery Systems

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Liposomes are lipid-based nanocarriers that were introduced as medication delivery devices in the 1970s. Recent significant advancements in liposome technology have rekindled interest in their application as effective antibiotic delivery systems for antimicrobial-resistant bacteria (ARB)[26, 27].

The FDA approved the antibiotic-liposome medication Arikayce in 2018 for the treatment of lung illness caused by bacteria from the *M. avium* complex[28]. Due to their structural similarity to bacterial cell membranes, liposomes possess a unique ability to fuse with the bacterial membrane, allowing large quantities of antibiotics to be transported directly into the bacterial cell. This property is at the heart of an innovative technology known as liposome-bacterial fusion, which offers a promising solution to the challenges of non-enzyme-dependent antibiotic resistance in many clinical strains of *Pseudomonas aeruginosa*. The resistance of these strains is often due to reduced specific permeability of the outer membrane, the activity of counter-efflux pumps, or both. (Figure 3)[29]. Furthermore, this technology also offers the potential to address resistance patterns associated with enzyme-mediated antibiotic degradation by encapsulating antibiotics within liposomes to protect them from enzyme inhibition[30]. Moreover, studies have shown that encapsulating the antibiotic piperacillin within liposomes composed of phosphatidylcholine and cholesterol helped protect it from degradation by beta-lactamase enzymes secreted by some *Staphylococcus spp.* This reflects the potential of liposome-based delivery systems to maintain antibiotic efficacy for longer periods and reduce the need for dose increases, contributing to improved therapeutic response and reduced side effects associated with conventional treatment [31, 32].

Smart biopolymer-based systems use biomaterials such as chitosan, alginate, or gelatin, which are biodegradable and highly biocompatible. These systems allow for prolonged local delivery, making them suitable for treating chronic infections such as osteomyelitis or bacterial biofilms, which are difficult to reach with traditional antibiotics alone[33, 34].

5. Developing Alternatives to Antibiotics

With the growing threat of bacterial resistance to traditional antibiotics, there is an urgent need to develop effective and safe alternatives that can replace or enhance the effectiveness of traditional antibiotics[35]. This approach aims to reduce selective pressure on bacteria and prevent the development of resistant strains[35]. Potential alternatives include Phage therapy, immunotherapies, antimicrobial peptides (AMPs), bacteriophages, plant extracts, nanocomposites, and strategies to modify microbiome balance, as illustrated in (Figure 4)[36] .

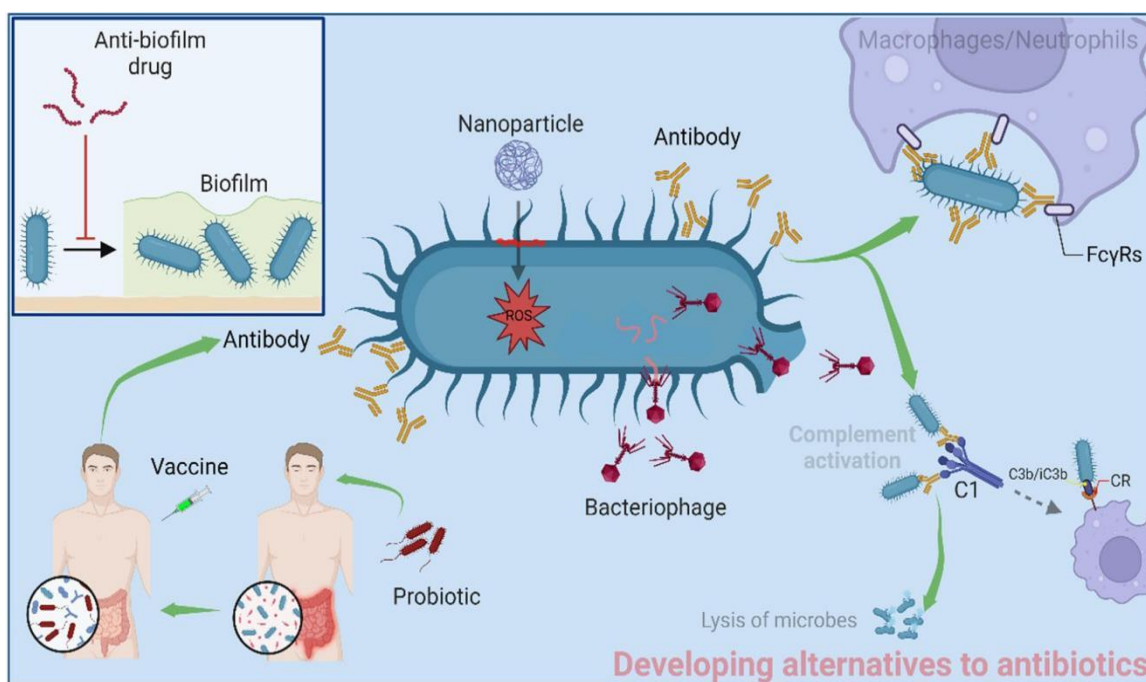


Figure 4. Alternatives to antibiotics



5.1 Phage therapy

Research into bacteriophages began in the early 20th century and has attracted significant interest due to their ability to accurately identify and kill target bacteria without affecting the body's beneficial microbes. They are characterized by their aggressive lytic cycle, where they bind to bacteria, insert their genetic material, and replicate within them until they lyse and release new copies of phages[37].

Phages execute their lytic cycle through several stages, primarily by employing endolysins, enzymes that lyse bacteria by degrading peptidoglycan [38]. Endolysins can be engineered for selectivity towards several species of Gram-negative and Gram-positive bacteria. A study identified four recombinant endolysins capable of efficiently lysing one hundred Gram-negative bacterial pathogens, including multidrug-resistant *Klebsiella pneumoniae*, *Salmonella*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii*, and *Enterobacter species* strains[39].

Historically used as an alternative treatment before the advent of antibiotics, phages continue to be used clinically in countries such as Georgia and Russia. They have been used experimentally to combat resistant bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, resulting in significant reductions in bacterial numbers and significant improvements in animal models (such as rats and mice), with a survival rate of up to 100% after just a single dose[39].

Phages also demonstrated a high ability to penetrate the biofilm (the biological margins that protect bacteria) and dismantle its matrix thanks to special enzymes known as lysins or polymerases (enzymotics), which enhances the effectiveness of treatment, especially when combined with antibiotics[40].

5.2 Biofilm

Biofilms are one of the most significant challenges in treating chronic bacterial infections, as they provide a protected environment that inhibits the effectiveness of antibiotics and promotes bacterial resistance to treatment[41]. This process typically begins with bacterial adhesion to surfaces, a pivotal step in biofilm formation, making targeting this early stage a promising strategy



for prevention and treatment. Among the most prominent molecules that have demonstrated effectiveness in this context are mannosides, which bind to the bacterial adhesion receptor FimH, present in pathogenic *Escherichia coli*. Laboratory and animal studies have demonstrated their ability to inhibit biofilm formation and prevent cell invasion[42].

Other adhesion components, such as antigen 43 and curli fibrils, also play a key role in anchoring bacteria to surfaces. This has led to the development of compounds such as FN075 and BibC6, which inhibit curli fibril biosynthesis by inhibiting vital intracellular pathways. Furthermore, anti-biofilm peptides have emerged as innovative solutions, the most notable of which are IDR-1018, DJK-5, and DJK-6, which degrade ppGpp, a regulatory nucleotide that plays a key role in resistance to nutritional stress and antibiotics[43].

Phages—specifically, the enzymes they secrete, such as depolymerases—have also demonstrated an effective ability to degrade the outer polymers that make up biofilms, helping to dismantle this protective structure, as observed in the inhibition of *Acinetobacter baumannii* colonization on medical surfaces[44].

Another recent trend is the use of aptamers, short DNA or RNA molecules designed to selectively bind to bacterial surface components such as flagella or surface sugars. Some have been shown to have a remarkable ability to inhibit biofilm formation, especially when combined with drug delivery vehicles such as liposomes carrying antibiotics[45]. Together, these techniques represent a multi-pronged approach to combating biofilm infections, a promising step in the face of the growing challenges of resistance to traditional antibiotics.

5.3 Probiotics

Probiotics are defined as beneficial live microorganisms, usually *Lactobacillus* or *Bifidobacterium* strains, administered to the host at appropriate concentrations to promote microbial balance and achieve health effects[46]. Probiotic supplementation has become widely accepted as a general health support option, despite limited conclusive evidence regarding their purported effects. Currently understood mechanisms suggest that probiotics exert their protective effects by regulating immune responses, strengthening the intestinal epithelial barrier, competing



with pathogenic microbes for nutrients, and directly secreting antibacterial compounds such as bacteriocins[47]. However, the probiotics provide health benefits, are not a direct replacement for antibiotics, and being used in some cases, particularly for conditions like diarrhea and irritable bowel syndrome[48].

The microbiome's ability to prevent the colonization and spread of pathogens is known as "colonization resistance," and it is one of the most important natural defense mechanisms enhanced by probiotics[49]. For example, *Bacillus subtilis*, a common gut microbe used in probiotic formulations, has been shown to produce bacitracin, which inhibits cell wall synthesis in Gram-positive bacteria such as MRSA[50]. While bacitracin has been shown to be effective in this context, a comparative clinical study demonstrated that mupirocin outperformed it in reducing *Staphylococcus aureus* colonization in the nose. Additionally, *B. subtilis* produces fengycins, lipopeptides that have been shown to be effective in disrupting the Agr system essential for *Staphylococcus aureus* colonization, highlighting its potential as a preventative probiotic option[51].

In addition to natural probiotics, a recent trend has emerged toward the use of genetically engineered probiotics. A probiotic based on *Escherichia coli* Nissle 1917 was developed, equipped with sensors and specific analysis devices. It was able to identify and kill *Pseudomonas aeruginosa* bacteria by 99% and reduce biofilm formation by up to 90% in laboratory models. This efficacy was also demonstrated in animal models[52]. These developments open up promising avenues for the use of probiotics as a therapeutic agent for colonization resistance and infection prevention, although their clinical use remains limited pending further testing and scientific validation[53].

5.4 Nanotechnology in Antimicrobial Therapy

Nanotechnology has revolutionized medicine, particularly in the development of new and effective strategies to combat microbial infections, especially in light of the global increase in resistance to traditional antibiotics[54]. Nanomaterials possess unique physical and chemical properties, such as small size, high surface area, and the ability to directly interact with bacterial cell walls, making them promising tools for designing innovative antimicrobials[55].



Silver nanoparticles (AgNPs) have demonstrated potent activity against a wide range of Gram-positive and Gram-negative bacteria, acting through multiple mechanisms including cell membrane penetration, generation of ROS, and inhibition of essential proteins and enzymes in the cell [56]. Gold nanoparticles (AuNPs) are also being used as smart antibiotic delivery systems, improving drug concentration at the site of infection and reducing side effects[57]. These single-element nanoparticles have antibacterial activity that is not targeted, whereas the development of composite nanoparticles has the potential to boost specificity and lower the amount of damage done to microbiota[58]. Gold nanocomposite particles with a narrow spectrum antibacterial activity and a gram-positive antibacterial action were created [59]. These particles were derived from amino sugars and were created to address the structural variations in the cell membrane between gram-positive and gram-negative bacteria. Research indicated that nanoparticles composed of graphene oxide-silver (GO-Ag) shown specific inhibitory effects on gram-negative *E. coli* and gram-positive *S. aureus*[60]. Hybrid nano-systems have also been developed that combine conventional antibiotics with nano-materials, enhancing antibacterial efficacy and reducing the likelihood of resistance development[61]. In addition to pharmaceutical applications, nanotechnology is being used in the design of antibacterial biofilms, nano-wound dressings, and biosensing systems for early detection of infections[62, 63]. However, despite these promising results, concerns remain about the potential cytotoxicity of nano-materials and their unintended effects on host tissues and beneficial microbes. The small size and high reactivity of nanoparticles, which make them effective against pathogens, may also cause oxidative stress, inflammation, or genotoxicity in human cells [64]. Furthermore, the environmental accumulation of nanoparticles, especially silver and metallic nanoparticles, raises questions about their ecotoxicity and long-term sustainability[65]. Despite the benefits of nanoparticles, further studies are needed on the safety profiles of nanoparticles.

5.5 Immunotherapies and Immunomodulation

Immunotherapies are one of the most prominent emerging trends in modern medicine. They rely on stimulating or modifying the patient's immune system to eliminate disease-causing agents, whether cancer cells, pathogens, or chronic inflammatory conditions[66]. The concept of immunotherapy focuses on the use of multiple tools, such as monoclonal antibodies, modified



immune cells (such as CAR-T cells), and immunovaccines, to stimulate a specific and effective immune response[67].

Immune modulation refers to the reprogramming of the immune system to achieve a delicate balance between stimulation and suppression[68]. In some cases, immune activity can be enhanced to fight infection or tumors, while in other cases (such as autoimmune diseases), excessive immune activity must be suppressed to reduce tissue damage. Immunotherapies have shown significant progress in several areas, most notably cancer treatment, where several immunotherapies, such as checkpoint inhibitors, have been approved as first-line treatments. In contrast, immunomodulation has emerged as an effective tool in treating chronic inflammatory diseases such as lupus and multiple sclerosis, by modulating cytokine production or inhibiting pathologically active T cells[69].

5.6 Natural Remedies and Plant Extracts

Natural remedies, particularly plant extracts, have gained increasing attention in research and medicine as effective alternatives or complements to conventional antibiotics, especially in light of the growing phenomenon of bacterial resistance. Medicinal plants contain a wide range of active compounds such as flavonoids, phenols, alkaloids, and terpenoids, which have antibacterial, anti-inflammatory, and antioxidant properties[70].

Numerous studies have shown that plant extracts such as garlic (*Allium sativum*)[71], ginger (*Zingiber officinale*)[72-75], and cinnamon (*Cinnamomum spp.*)[76, 77] are capable of inhibiting the growth of dangerous bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. This effectiveness is attributed to their ability to damage bacterial cell membranes and interfere with vital intracellular processes such as protein and DNA synthesis[78]. In addition, some plant extracts have been shown to disrupt the quorum sensing system, which bacteria use to communicate and form biofilms, making them more susceptible to treatment. Some plant compounds also exhibit a synergistic effect with antibiotics, improving their effectiveness and reducing the required dosage, thus limiting side effects and delaying the emergence of resistance.



CONCLUSION

Antibiotic resistance poses a multidimensional threat that challenges modern medicine, public health, and global development. While the roots of the crisis lie in decades of antibiotic misuse and scientific stagnation, solutions must be innovative, multidisciplinary, and systemic. The following sections of this review will explore these emerging solutions in depth, assessing their potential to reshape the treatment landscape for infectious diseases in an era where traditional antibiotics alone are no longer sufficient.

Conflict of interests

There are non-conflicts of interest.

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الخلاصة

تُمثل العدوى الناتجة عن البكتيريا المقاومة للمضادات الحيوية (ARB) مصدر قلق صحي عالمي رئيسي في عصرنا. إلى جانب تطوير مضادات حيوية جديدة، يُمثل تحديد الكائنات الدقيقة المقاومة للمضادات الحيوية واستكشاف بدائل للأدوية الحالية استراتيجيات فعّالة لمعالجة مقاومة المضادات الحيوية. يُجمع هذا التحليل الحلول الواعدة لمكافحة مقاومة المضادات الحيوية التي لا تزال قيد التطوير. تشمل هذه الاستراتيجيات: (أ) اكتشاف مضادات حيوية جديدة من خلال تعديل المركبات الحالية؛ (ب) تعزيز فعالية المضادات الحيوية الحالية من خلال التحفيز الأيضي أو تطبيق أنظمة توصيل متقدمة؛ (ج) ظهور بدائل جديدة للمضادات الحيوية التقليدية، بما في ذلك العاثيات والإندوليسينات، ومركبات مضادة للأغشية الحيوية، والبروبيوتيك، والمواد النانوية، واللقاحات، والعلاجات القائمة على الأجسام المضادة. تشير الدراسات السريرية وقبل السريرية إلى أن هذه العلاجات تتمتع بإمكانيات كبيرة ضد الكائنات الدقيقة المقاومة للمضادات الحيوية. ومن المتوقع أن تصبح بعض منتجات مقاومة المضادات الحيوية متاحة تجاريًا في المستقبل القريب.

الكلمات المفتاحية: المضادات الحيوية، والطرق البديلة، والبكتيريا المقاومة