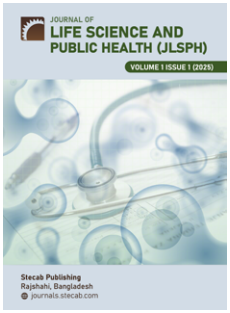

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Review Article

Antimicrobial Resistance (AMR): Chemistry Solutions Beyond Traditional Antibiotics

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About Article

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as the most critical threat to global health, contributing to over 1.2 million deaths annually and projected to cause up to 10 million deaths per year by 2050 if left unaddressed. Traditional antibiotic development focused on structural modification of existing molecules has failed to match the rapid evolution of resistance mechanisms. This review underscores a paradigm shift, positioning chemistry not as a supplementary tool but as a transformative force in AMR mitigation. We explore a spectrum of chemistry-driven strategies, including efflux pump inhibitors that restore antibiotic efficacy by over 80% in vitro, β-lactamase inhibitors with 50–90% re-sensitization capacity, and antisense oligonucleotides demonstrating >70% gene silencing efficiency for resistance determinants like blaCTX-M and ndm-1. Novel CRISPR-based antimicrobials delivered via chemically engineered nanoparticles have shown the potential to restore colistin susceptibility in >60% of resistant strains. Furthermore, smart nanomaterials and targeted delivery systems have achieved up to 5-fold increases in localized drug concentration, significantly reducing off-target effects. These precision-based approaches enabled by synthetic chemistry, materials science, and molecular engineering offer versatile, adaptable, and resistance-mitigating solutions. We highlight regulatory challenges, scalability concerns, and the imperative for interdisciplinary collaboration to bridge lab innovations with clinical implementation. Chemistry remains central in the quest for sustainable, long-term solutions to AMR.

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1. INTRODUCTION

Antimicrobial resistance (AMR) is becoming a bigger and bigger challenge to modern medicine, putting its entire foundation at risk. This growing worldwide health catastrophe is happening because germs like bacteria, viruses, fungus, and parasites may now resist therapies that used to work. AMR is already responsible for over 1.2 million deaths per year, and if nothing is done quickly, it might kill up to 10 million people every year by 2050 (Antimicrobial Resistance, n.d.). The World Health Organization (WHO) has put AMR in the top ten global health problems since they know how serious it is (10 Global Health Issues to Track in 2021, n.d.). The main cause of this problem is that antibiotics are becoming less and less effective because they are being misused, overused, and contaminated by the environment. The most important reason is that microorganisms are constantly evolving new ways to resist them (Lawal, *et al.*, 2024).

Finding new antibiotics has mostly stopped in the last few decades. The time between the 1940s and 1970s, which is commonly called the "golden era," saw the discovery of many different types of antibiotics from natural sources such actinomycetes. Tetracyclines, macrolides, aminoglycosides, and β-lactams were some of these (Hughes & Karlén, 2014). But modern attempts have been hurt by "target fatigue," which happens when researchers keep looking at the same small number of bacterial targets. This often leads to little changes in known medications instead of completely new ones. To make things worse, bacteria have developed advanced ways to resist drugs, such as efflux pumps, enzymatic degradation (like β-lactamases), target site alteration (like methylation of rRNA), and biofilm formation. Horizontal gene transfer can quickly spread these resistant traits between species, making them very hard to control (Vivekanandan *et al.*, 2025).

Chemistry has become a promising way to find new solutions, even though many problems are hard to solve. Antimicrobial peptides (AMPs) and their synthesized versions use membrane-disrupting effects and can be chemically adjusted to make them more stable and selective. Quorum-sensing inhibitors (QSIs) are a type of antivirulence compound that stop pathogens from working without killing them. This lowers the selective pressure for resistance (Helmy *et al.*, 2023). Metal-based agents, such ruthenium (II) complexes and silver nanoparticles, work in different ways, such as producing reactive oxygen species (ROS) and interfering with membranes. Also, even though CRISPR-Cas systems come from biology, their therapeutic potential depends a lot on chemistry for delivery through lipid nanoparticles, conjugated polymers, and other carriers. This lets focused gene editing get rid of resistant bacteria (Zeng *et al.*, 2017). Chemical biology methods like small-molecule probes and high-throughput screens are also very important for finding new antibacterial targets and figuring out how resistance works at the systems level.

The goal of this review is to give a full and forward-looking look into chemical developments that go beyond the usual ways of making antibiotics. We look at a number of new techniques, such as antivirulence drugs, AMPs, metal-based therapies, nanotechnology-enabled treatments, gene-editing platforms, and combination approaches, by looking at their molecular design and how well they may be used in real life. The focus is on approaches that make medications more selective, allow them to be delivered to specific areas, get beyond resistance, and work better with other drugs. We also stress how important analytical and computational chemistry are for speeding up the discovery of new drugs and the development of new diagnostic tests.

This analysis shows that chemistry is not just a supporting science, but also a driving force behind new ideas and technical advancements in the fight against AMR. Chemistry is in a unique position to assist change the way we stop and treat infectious diseases by combining knowledge of chemicals with knowledge of how things work and working with people from other fields. Figure 1 shows a conceptual picture of the range of unusual chemical methods that are being looked at to fight AMR.

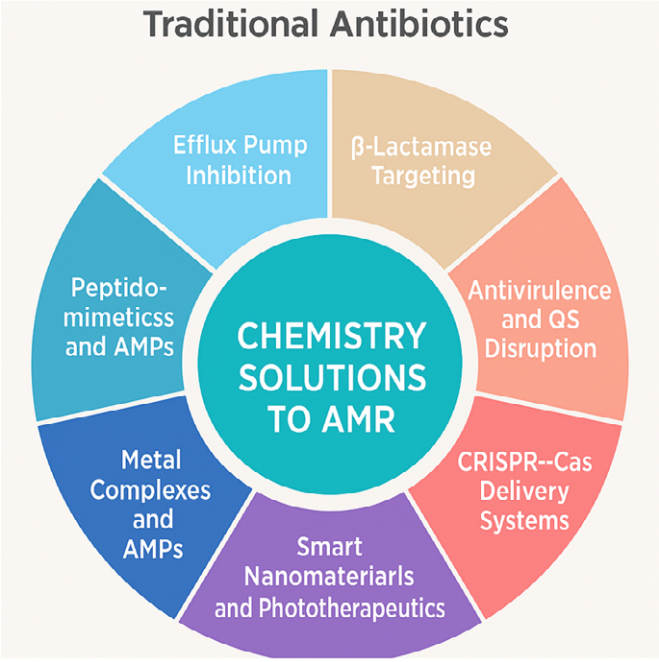

Figure 1. Chemistry-Driven Strategies to Combat AMR Beyond Traditional Antibiotics.

This schematic illustrates key chemistry-guided strategies for addressing antimicrobial resistance (AMR) beyond the scope of traditional antibiotic therapies. The diagram highlights several distinct modalities, including inhibition of efflux pumps, targeting of β-lactamases, delivery systems for CRISPR–Cas technologies, disruption of quorum sensing and virulence pathways, application of smart nanomaterials and light-activated therapeutics, use of metal-based complexes, and design of synthetic antimicrobial peptides. Collectively, these approaches demonstrate the multifaceted role of chemistry in influencing microbial behavior, circumventing resistance, and enabling targeted antimicrobial interventions.

2. LITERATURE REVIEW

2.1. Redefining antimicrobial strategy through chemistry

Many medications that were once effective are now rendered obsolete due to the global rise of antimicrobial resistance (AMR) in clinical and environmental settings. This alarming trend has

necessitated a shift from incremental antibiotic modification to the development of radical, chemistry-driven alternatives. Although promising chemical strategies have emerged, several critical gaps remain unaddressed in existing research (Murugaiyan *et al.*, 2022).

For example, while efflux pump inhibitors (EPIs) such as phenylpiperazines and peptidomimetics have shown enhanced in vitro potency, most studies fail to demonstrate consistent in vivo efficacy or pharmacokinetic stability, limiting their clinical translation. Similarly, β-lactamase inhibitors like avibactam and vaborbactam have improved treatment options against resistant strains; however, resistance to these inhibitors is already emerging, highlighting the lack of long-term durability in these solutions (Gaurav *et al.*, 2023).

The application of antisense oligonucleotides and peptide nucleic acids (PNAs) presents a compelling method to silence resistance genes. Yet, most research remains in preclinical stages, and delivery mechanisms across diverse bacterial species remain inconsistent, representing a critical technological barrier. Likewise, CRISPR–Cas systems have shown great potential, but few studies have addressed the risk of off-target gene editing or immune activation, raising safety and specificity concerns for human applications (Duffey *et al.*, 2024).

Precision antimicrobial platforms such as siderophore–antibiotic conjugates (e.g., cefiderocol) offer targeted therapy, but clinical trials have yielded mixed results, partly due to heterogeneity in bacterial uptake mechanisms and lack of biomarker-based patient selection. Additionally, the scalability and reproducibility of dual-functional molecules, stimuli-responsive systems, and aptamer-based therapies remain largely untested beyond laboratory settings (Ayomide *et al.*, 2024; Le Terrier *et al.*, n.d.).

Quorum sensing inhibitors (QSIs) and antivirulence agents provide a non-lethal approach to disarming pathogens. However, many QSIs lack robust structure–activity relationship (SAR) models, and most studies have not evaluated the risk of bacterial adaptation or compensatory virulence pathways. Likewise, small-molecule inhibitors of secretion systems and biofilm disruptors show promise, but there is insufficient long-term data on resistance development or toxicity in complex host environments.

Antimicrobial peptides (AMPs) and their mimetics offer broad-spectrum activity, but current designs often suffer from poor bioavailability, serum instability, and host cytotoxicity, impeding their real-world use. Moreover, metal-based agents and phototherapeutics have demonstrated antimicrobial effects in vitro, yet systemic toxicity and off-target ROS generation remain critical challenges that must be addressed before clinical application.

Finally, while synergistic drug combinations and AI-guided therapy design represent cutting-edge strategies, there is a lack of standardized frameworks for predicting, validating, and monitoring synergy in vivo, creating a disconnect between computational predictions and therapeutic outcomes (Du *et al.*, 2025).

2.2. CRISPR-Cas-based approaches: Chemical delivery systems

CRISPR-based tools like Cas9 and Cas13 provide exceptional precision in targeting and removing resistance genes, especially those carried on plasmids. Yet, delivering these systems effectively into bacterial cells remains a significant hurdle. Recent advances in chemistry have led to the creation of novel delivery vehicles, including phagemids, cationic lipid nanoparticles, and engineered polymers. A notable example involves lipidoid nanoparticles, which have been successfully used to transport Cas13 into bacteria and silence the mcr-1 gene, restoring their sensitivity to colistin (Agha *et al.*, 2025). Other delivery techniques, such as DNA carriers attached to dendrimers, make the process more stable and easier to take in. Collectively, these hybrid systems underscore the relevance of chemical methods in enabling gene-editing platforms to restore antibiotic efficacy.

2.2.1. Precision antimicrobial platforms

2.2.1.1. Ligand-targeted antimicrobial conjugates (e.g., Siderophore–antibiotic hybrids)

One good technique to selectively target bacteria is to use their need for iron uptake mechanisms. Siderophore-antibiotic conjugates like cefiderocol operate like iron-binding agents, tricking bacteria into bringing in the antibiotic by looking like natural siderophores. This "Trojan horse" method has been improved to make sure that the medicine is released inside the bacterial cell. Chemists have been working on making cleavable linkers that only respond to certain things, including changes in pH or the presence of bacterial enzymes, so that the antibiotic only works where the infection is (Negash *et al.*, 2019). Figure 2 illustrates the mechanism of targeted drug

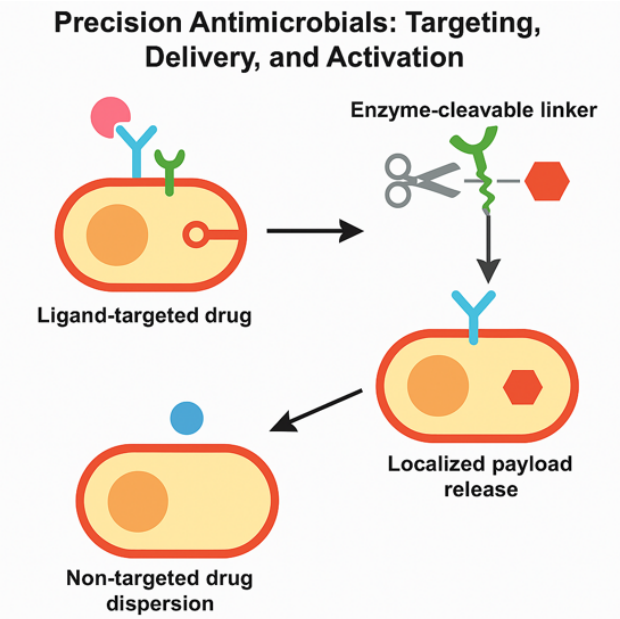

Figure 2. Precision antimicrobials: mechanisms of targeted vs. Non-targeted delivery and activation

delivery in comparison to non-specific dispersion, which often results in suboptimal therapeutic concentrations.

This figure shows how antibiotic administration works using receptors. In the top panel, a drug–ligand combination first attaches to a specific receptor on the surface of the bacteria. Once within the cell, a specifically designed linker that can be broken down by bacterial enzymes breaks down, delivering the active medicine right at the site of infection. The lower panel shows how this is different from untargeted distribution, when the medicine spreads out widely, which could make it less effective and expose people to it more. The contrast shows how chemically tailored targeting methods can make treatments more accurate, lower side effects, and increase overall therapeutic results.

2.2.1.2. Dual-functional molecules: Binding + delivery

Dual-function antimicrobial agents are made to do two things: attack bacterial cells very specifically and deliver therapeutic ingredients. Some examples are folate-conjugated antibiotics that target Staphylococcus aureus more than other bacteria and mannosylated peptides that bind to bacterial lectins. These structures are often put together using modular methods like solid-phase peptide synthesis or click chemistry. More advanced versions are made with amphiphilic properties, which let them form micelles on their own. Micelles can help drugs dissolve better, improve their pharmacokinetic profiles, and make it easier for cells to take them up (Hussien *et al.*, n.d.).

2.2.1.3. Stimuli-responsive systems

Stimuli-responsive antimicrobial materials are made to only work when they get signals that are particular to infections. For example, pH-sensitive polymers can release antibiotics in the acidic conditions often seen at infection sites, while enzyme-responsive systems are triggered by bacterial enzymes like gelatinases. Redox-sensitive hydrogels with disulfide connections also break down in oxidative conditions, which is another sign of infected tissue. This lets drugs be released in a regulated way. By responding to these targeted biochemical cues, chemically engineered systems lower the amount of drugs that the whole body is exposed to and make antimicrobial therapy more precise (Wang *et al.*, 2022).

2.2.1.4. Aptamer–antibiotic chimeras

Aptamers are short, man-made strands of nucleic acids that are made to stick to bacterial surface proteins very tightly. When used with antibiotics, they let you deliver drugs directly to harmful bacteria without harming helpful bacteria. For instance, DNA aptamers that bind to outer membrane proteins in Pseudomonas aeruginosa have been successfully connected to antibiotics like ciprofloxacin and chloramphenicol. You can make these delivery systems even better by adding PEGylation or custom linkers to make the drug stay in the body longer and lower the risk of immunological responses (Hassibian *et al.*, 2025).

2.2.2. Antivirulence and Quorum Sensing Inhibitors (QSIs)

2.2.2.1. Chemical disruption of quorum sensing

Quorum sensing (QS) is very important for controlling the growth of biofilms, the pathogenicity of bacteria, and Bacterial communication systems, such as quorum sensing (QS), are very important in the development of resistance. Furanones, thiolactones, and brominated lactones are among artificial substances that mess up this communication by acting like natural signaling molecules like AHLs and AI-2. These chemicals stop the signaling cascade by competing for binding at QS receptors. High-throughput screening of chemical libraries has resulted to the discovery of several potent quorum sensing inhibitors (QSIs), particularly those that target LuxR-type proteins, with some demonstrating inhibitory activity at nanomolar concentrations (Alum *et al.*, 2025).

2.2.2.2. Small-Molecule QSIs: SAR and Mechanistic Insight

Structure-guided techniques have been very important in making quorum sensing (QS) antagonists that work very well and have the best physicochemical properties (Okafor *et al.*, 2025). For example, diketopiperazine-based compounds stop LasR-mediated signaling in Pseudomonas aeruginosa, and isothiocyanates mess up the Agr communication system in Staphylococcus aureus. Structure–activity relationship (SAR) studies show that factors like halogen substitution, alkyl chain length, and hydrogen-bonding potential have a big effect on both binding affinity and target specificity. QS inhibitors can not only make bacteria less harmful, but they can also make them more vulnerable to the immune system of the host and make regular antibiotics work better (Sully *et al.*, 2014).

2.2.2.3. Virulence Factor Inhibitors

Using chemical inhibitors to target bacterial secretion systems like Type III (T3SS) and Type VI (T6SS) is a promising way to fight viruses. Salicylidene acylhydrazides and other molecules have been proven to stop pathogens like Salmonella and Shigella from making injectisomes. High-throughput screening has also found small-molecule inhibitors that work against important virulence factors, such as the toxins made by Clostridium difficile and the hemolysins made by Staphylococcus aureus (Morgan *et al.*, 2018).

2.2.2.4. Anti-biofilm strategies

Biofilms protect bacteria by making them much less likely to be harmed by antibiotics and the immune system. Researchers have produced chemical agents that help biofilm spread, such as nitric oxide donors, c-di-GMP inhibitors, and enzymes like dispersin B that break down biofilm matrix. In addition, scientists have produced tiny compounds like 2-aminoimidazoles and brominated phenols that stop biofilm growth and signaling pathways. These molecules often do this without hurting neighboring healthy cells (Abdelhamid & Yousef, 2023).

2.2.3. Synthetic and semi-synthetic antimicrobial peptides (AMPs)

2.2.3.1. Rational peptide design

Antimicrobial peptides (AMPs) work by disrupting bacterial membranes or targeting essential processes inside the cell (Elechi *et al.*, 2025). Through rational design, researchers have improved their potency and stability using strategies like stabilizing α-helical structures, optimizing cationic residues,

and substituting D-amino acids to resist degradation. Notable examples include modified versions of the human peptide LL-37 and synthetic peptides like Pexiganan, which show strong antimicrobial activity and improved performance in biological environments (Mwangi *et al.*, 2023).

2.2.3.2. Peptidomimetics and foldamers

Peptidomimetics, like β-peptides, γ-AApeptides, and peptoids, are made to be resistant to proteases while keeping important properties such a positive charge and the ability to behave as an amphiphile. Some, like helical foldamers, do a good job of copying the structure of natural antimicrobial peptides (AMPs) yet have better pharmacokinetics. Another way is to use stapled peptides, which add covalent crosslinks to make α-helical shapes more stable. This not only makes them stick better to biological targets, but it also makes them harder to break down by enzymes (Méndez-Samperio, 2014).

2.2.3.3. Supramolecular Chemistry of AMPs

Antimicrobial peptides (AMPs) can form nanostructures like micelles or nanofibers on their own. This makes it easier for them to interact with bacterial membranes and lets drugs be released in a regulated way. Peptide amphiphiles and co-assembled complexes are examples of systems that help multivalent binding to bacterial surfaces, which makes antimicrobial agents stronger. Researchers may make these materials work better by carefully changing their chemical makeup, notably the balance between hydrophobic and hydrophilic areas. This will allow them to preferentially break up bacterial cells while causing the least amount of damage to host tissues (Teixeira *et al.*, 2020).

2.2.3.4. AMP–Nanoparticle Hybrids

By attaching antimicrobial peptides (AMPs) to metallic nanoparticles like silver or gold or to polymeric carriers, they can be delivered to specific places and stay there for a long time. This method increases the concentration of drugs in the area, which makes them more effective and less harmful to the body as a whole. In addition to breaking apart bacterial membranes, these hybrid systems often use other methods, such as generating reactive oxygen species (ROS) and photothermal effects, to make antimicrobial action even stronger (Fadaka *et al.*, 2021).

2.2.4. Metal-based and phototherapeutic platforms

2.2.4.1. Metal complexes with tunable ligands

Advances in coordination chemistry have enabled the design of metal complexes with tailored ligand environments that enhance antimicrobial efficacy. For instance, Ru(II) complexes bearing polypyridyl ligands are capable of intercalating bacterial DNA and perturbing intracellular redox homeostasis (Lawal *et al.*, 2024). Ag(I) and Cu(II) complexes, in contrast, frequently exhibit multi-target activity disrupting bacterial membranes while simultaneously inhibiting essential enzymes. This multi-mechanistic mode of action positions metal-based antimicrobials as a particularly promising avenue for therapeutic development.

2.2.4.2. Light-activated antimicrobials

Photodynamic treatment (PDT) uses photosensitizers that are activated by light to create reactive oxygen species (ROS) that can kill and hurt bacterial cells. Porphyrins, phthalocyanines, and BODIPY derivatives are all common photosensitizer scaffolds. They are all recognized for being able to absorb a lot of light and produce ROS quickly. To make them more precise, these agents can be chemically attached to targeting molecules or added to delivery systems. This lets them be activated at specific sites, which is highly helpful for treating infections that are deep inside tissues (Fadaka *et al.*, 2021).

2.2.4.2. Photo-switchable antibiotics

Antibiotics modified with light-responsive groups like azobenzene or diarylethene allow for reversible activation using light. This approach provides precise spatiotemporal control over antimicrobial activity, helping to minimize systemic toxicity and reduce selective pressure for resistance (Sarabando *et al.*, 2023).

2.2.4.3. Synergistic redox modulators

Metal complexes can work in concert with traditional antibiotics by triggering oxidative stress in bacterial cells. For instance, Cu(II) phenanthroline compounds have been found to boost the activity of β-lactam antibiotics by increasing reactive oxygen species (ROS) levels and disrupting bacterial membrane structure. This combined mode of action offers a promising approach to re-sensitize resistant bacterial strains to drugs that have otherwise lost their effectiveness (Sharma *et al.*, 2022).

2.2.5. Smart nanomaterials and hybrid constructs

2.2.5.1. ROS-Generating Nanostructures

Metal-organic frameworks (MOFs) and graphene oxide-based hybrids show strong antimicrobial effects by generating reactive oxygen species (ROS) and disrupting bacterial membranes. These nanomaterials can be tailored by incorporating metal ions or loading them with antibiotics, and their activity can be activated by environmental triggers like pH shifts or light exposure. These properties make them highly adaptable platforms for targeted, stimuli-responsive antimicrobial treatments (Li *et al.*, 2025).

2.2.5.2. Stimuli-responsive antimicrobials

Smart materials—such as temperature-sensitive hydrogels, enzyme-responsive polymers, and redox-triggered vesicles—are specifically designed to release antimicrobial agents in response to infection-related physiological signals. These systems react to cues like increased temperature, the presence of specific enzymes, or oxidative stress, enabling precise, localized drug delivery and reducing unwanted effects on surrounding healthy tissue (Ding *et al.*, 2025).

2.2.5.3. Covalent Organic Frameworks (COFs)

Covalent organic frameworks (COFs) are highly porous and structurally tunable materials, making them well-suited for antimicrobial delivery applications. Functionalization with antibiotics or cationic groups allows these frameworks to exert direct bactericidal activity while enabling controlled and sustained drug release over extended periods (Bedair *et al.*, 2024).

2.2.5.4. Phage–nanomaterial hybrids

Engineering phage particles with nanoparticles or polymers can boost their infectivity, stability, and ability to target specific bacteria. These hybrid systems are especially versatile. They can carry genetic tools like CRISPR as well as traditional antimicrobial agents, making them powerful tools in the fight against resistant infections (Lawal *et al.*, 2025).

2.2.6. Drug repurposing and synergistic combinations

2.2.6.1. Repurposed non-antibiotics

A number of clinically approved drugs—such as chloroquine, sertraline, and doxorubicin—have shown antimicrobial effects by interfering with bacterial membranes or inhibiting efflux pump activity. By applying chemical reformulation techniques like nanoencapsulation or drug conjugation, their pharmacokinetic properties can be improved to enhance targeted delivery and minimize side effects. These developments underscore the potential of repurposing existing medications as effective treatments for infectious diseases (Gaurav *et al.*, 2023).

2.2.6.2. Antibiotic–inhibitor hybrids

The chemical conjugation of antibiotics with adjuvants such as β-lactamase inhibitors or efflux pump inhibitors (EPIs) has facilitated the development of synergistic therapeutic agents. These hybrid constructs expand the antimicrobial spectrum and enhance efficacy, particularly against multidrug-resistant (MDR) bacterial strains (Kumar *et al.*, 2023).

2.2.6.3. Quantifying synergy

Techniques like checkerboard assays, isobolograms, and time-kill curves are commonly used to measure chemical synergy between antimicrobial agents. Structure–activity relationship (SAR)-guided combinatorial chemistry further supports the design and optimization of effective dual or triple-drug combinations (Bremmer *et al.*, 2016).

2.2.6.4. Computational design

Machine learning and molecular modeling now play a vital role in identifying synergistic drug combinations and refining antimicrobial therapy strategies. When integrated with chemistry-based databases, computational platforms like DeepSynergy and SynergyFinder support rational drug development by enabling large-scale screening and predictive analysis of how different antimicrobial agents interact. These tools are increasingly guiding the design of more effective combination treatments (Wu *et al.*, 2021).

3. METHODOLOGY

This review employed a structured and comprehensive literature analysis to explore non-traditional, chemistry-based strategies for addressing antimicrobial resistance (AMR). The methodology was designed to ensure the inclusion of high-quality, peer-reviewed, and clinically relevant sources, while adhering to ethical research standards applicable to secondary data analysis.

3.1. Data sources and search strategy

Data collection was performed using reputable academic databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search strategy utilized Boolean operators and keyword combinations such as:

- "chemical biology AND antimicrobial resistance",
- "nanomaterials for AMR",
- "efflux pump inhibitors",
- "CRISPR antimicrobials",
- "antivirulence chemical strategies".

The literature search was limited to articles published between 2010 and 2025, with a focus on the last 10 years to capture the most recent and impactful developments. Both original research and review articles were included.

3.2. Inclusion and exclusion criteria

To maintain relevance and quality, the following inclusion criteria were applied:

- Peer-reviewed publications or patents with clear experimental or clinical evidence,
- Chemical strategies with demonstrated antimicrobial or resistance-modifying activity,
- Research addressing real-world translational potential (e.g., delivery, toxicity, clinical trials).

Excluded were:

- Non-English language articles,
- Editorials or commentaries without primary data,
- Studies lacking reproducibility or with limited methodological transparency.

3.3. Data Extraction and analysis

Relevant information was systematically extracted, including:

- Type of chemical strategy or molecule,
- Target mechanism (e.g., efflux inhibition, gene silencing),
- Experimental models used (in vitro, in vivo, or clinical),
- Efficacy metrics (e.g., MIC reduction, gene knockdown efficiency),
- Toxicity or stability assessments.

Descriptive statistics were used to summarize trends in efficacy and delivery efficiency across therapeutic categories. Where applicable, meta-analytical indicators (e.g., response rates, fold-changes in drug susceptibility) from cited studies were included to support quantitative assessment.

3.4. Rationale for analytical approach

This review adopted a narrative synthesis approach, appropriate for integrating mechanistic, biological, and chemical insights across diverse study designs. Comparative evaluation of platforms (e.g., traditional antibiotics vs. CRISPR-loaded nanoparticles) was supported by contextual interpretation of experimental statistics reported in primary studies (e.g., IC_{50} values, % gene inhibition). No original statistical tests were performed, as this study relied on secondary data.

3.5. Ethical considerations

As this research involved only secondary analysis of published data, no human or animal subjects were directly involved. However, ethical principles were upheld by:

- Citing all sources appropriately,
- Respecting data privacy and authorship rights,

• Prioritizing studies that declared ethical approval and informed consent where applicable (e.g., in clinical trials referenced),

• Avoiding misrepresentation or manipulation of published data.

All data used in this review were publicly available through academic databases or open-access journals. Confidentiality, consent, and data protection were inherently respected through reliance on de-identified, published sources.

4. RESULTS AND DISCUSSION

Recent advancements in analytical chemistry, delivery systems, and chemical biology have significantly enhanced our ability to counteract antimicrobial resistance (AMR). This section presents a comparative and thematic analysis of the chemical tools and innovations accelerating AMR research and therapeutic development.

4.1. High-Throughput Screening (HTS): Broadening the Discovery Pipeline

High-throughput screening (HTS) techniques, particularly DNA-encoded libraries (DELs) and fragment-based lead discovery (FBLD), have expanded the chemical space accessible for AMR drug discovery. DELs enable simultaneous screening of billions of compounds, far surpassing traditional HTS capacities. When combined with next-generation sequencing, these libraries can rapidly identify high-affinity ligands for resistance enzymes such as β-lactamases or efflux pump regulators.

By contrast, FBLD excels in identifying small fragments that bind to cryptic or allosteric bacterial sites often missed by conventional ligands. Compared to DELs, FBLD offers fewer false positives and a better physicochemical profile for downstream drug development, though its lower initial binding affinities may require iterative optimization. Both approaches are complementary, and their integration could yield more robust lead compounds.

4.2. Analytical Tools and Chemical Methodologies Accelerating AMR Research

As antimicrobial resistance (AMR) continues to evolve faster than the development of conventional antibiotics, analytical chemistry has emerged as a driving force behind innovative countermeasures. Contemporary chemical techniques offer unparalleled precision in detecting resistance pathways, guiding the design of new therapeutics, and streamlining the path from discovery to clinical use. No longer limited to passive measurement, these methods now play an active role in shaping AMR research—enabling targeted diagnostics, real-time surveillance, and high-throughput screening that are critical for responding to rapidly emerging threats (Muteeb *et al.*, 2023).

High-Throughput Screening (HTS): DNA-Encoded Libraries and Fragment-Based Approaches

For a long time, high-throughput screening (HTS) has been a key aspect of finding novel antimicrobial treatments. But recent chemical discoveries have made it considerably more powerful. One new idea is DNA-encoded libraries (DELs), which attach a different DNA tag to each small molecule. This permits billions of molecules be tested at once on targets that are relevant to resistance, like efflux pumps, β-lactamases, and quorum-sensing regulators.

When used with next-generation sequencing, this method makes it possible to quickly find and enrich high-affinity binders through multiple rounds of selection(Peterson & Liu, 2023). Fragment-based lead discovery (FBLD) is a method that is becoming more and more useful. It uses small, low-molecular-weight chemical fragments to explore chemical space more effectively than standard drug-like compounds. These first fragment hits can be strategically improved by either lengthening the fragment or combining several fragments together to make stronger inhibitors that are more targeted. This technique frequently leads to fewer off-target effects and is especially helpful for targeting hard-to-reach places, like allosteric or cryptic enzyme pockets that are linked to antimicrobial resistance (Konaklieva & Plotkin, 2023).

4.3. Chemical probes for resistance detection

Accurately identifying specific resistance mechanisms is crucial for timely diagnosis and effective treatment. Over the years, chemists have made a lot of fluorogenic and chromogenic probes that only react to the enzymatic activity of major resistance-related proteins. These include metallo-β-lactamases (MBLs), serine β-lactamases, and enzymes that change aminoglycosides. For instance, active β-lactamases can cut fluorescent "turn-on" probes that have β-lactam structures. This makes a signal that can be seen in real time in both clinical samples and live bacterial cells. Also, unique probes have been made to find biofilm indicators such extracellular DNA, structural polysaccharides, and certain enzymes. These methods give us useful chemical information about the makeup and resilience of microbial communities (Yamin *et al.*, 2023).

4.4. Label-Free Biosensors and Surface-Enhanced Raman Spectroscopy (SERS)

Label-free methods that are fast, highly sensitive, and non-destructive—such as surface-enhanced Raman spectroscopy (SERS)—have significantly advanced the detection of bacterial pathogens and antimicrobial resistance. When bacterial cells are placed on nanostructured metal surfaces, often made from silver or gold nanoparticles, SERS dramatically boosts the Raman signals from cellular biomolecules. This allows for precise identification at the strain level and can reveal resistance-related traits, such as changes in membrane structure or metabolic function. In parallel, electrochemical biosensors that use immobilized chemical receptors or peptides are capable of directly identifying resistance genes like bla_{KPC}, mecA, and ndm-1, without requiring molecular labels. As these technologies continue to shrink into compact, user-friendly devices, the goal of real-time, point-of-care antimicrobial resistance diagnostics becomes increasingly attainable (Lawal *et al.*, 2025; Usman *et al.*, 2022).

4.5. Chemical Imaging of Antimicrobials In Vivo

Understanding the biodistribution of antimicrobial agents is essential for improving their effectiveness, especially in targeted or localized treatments. Recent progress in chemical

labeling has made it possible to attach radiotracers like ^18F and ^64Cu or MRI-active tags such as Gd(III) and ^19F to antimicrobial molecules. This enables real-time, non-invasive tracking using imaging techniques like positron emission tomography (PET) and magnetic resonance imaging (MRI). These advanced imaging tools offer detailed insights into how drugs are distributed, how deeply they penetrate tissues, and how they are cleared from the body—insights that traditional microbiological methods are unable to provide (Skwarczynski *et al.*, 2022). For example, positron emission tomography (PET) using ^18F-labeled rifampin analogs has been used to visualize how the drug accumulates in tuberculosis lesions. This approach has uncovered spatial differences in drug distribution, which may contribute to the emergence of resistance (Lawal *et al.*, 2025). In addition to speeding up drug development, these tools provide valuable opportunities to study microbial behavior and how infections respond to treatment. The integration of chemistry with biology, diagnostics, and materials science is leading to powerful new strategies that allow us to monitor, measure, and counteract antimicrobial resistance with unprecedented precision.

4.6. Challenges and translational barriers

Chemistry has made huge strides in the design of antimicrobial drugs, but getting non-traditional medicines into clinical use is still a big problem. Barriers like poor physicochemical qualities, safety concerns, complicated manufacturing methods, and unclear regulations still make it hard for new ideas to go from the lab to the clinic (Andrades-Lagos *et al.*, 2023).

4.7. Toxicity and immunogenicity of novel agents

A lot of the new chemical methods, such metal complexes, synthetic peptides, and nanoparticle-antibiotic hybrids, come with their own safety issues. These new antibiotics may produce dose-limiting toxicity, unexpected interactions with non-target tissues, or immunological responses, which is not the case with older small-molecule antibiotics (Parvin *et al.*, 2025). For example, metal-based antimicrobials such as ruthenium (II) or silver (I) complexes, along with certain cationic polymers, have shown potential to damage mammalian cells or disrupt the host microbiome if not precisely engineered. Likewise, peptide-based therapeutics and RNA delivery systems, such as lipid nanoparticles, have been linked to immune activation that can complicate systemic use. To mitigate these risks, early-stage development must prioritize detailed toxicological studies and careful structure–activity relationship optimization (de Oliveira *et al.*, 2024).

4.8. Stability and delivery barriers

Peptide, oligonucleotide, and nanomaterial-based therapies often face significant barriers in clinical use due to limited stability in vivo, rapid clearance, and susceptibility to degradation by serum enzymes. Chemical strategies such as PEGylation, backbone cyclization, and lipid conjugation can improve pharmacokinetics; however, they often bring new challenges related to synthesis complexity, manufacturing scalability, and regulatory hurdles. Localized delivery systems—including hydrogels, microneedles, and stimulus-responsive carriers—have demonstrated potential to enhance therapeutic precision. Yet, challenges persist regarding tissue penetration, dose uniformity, and reproducibility, especially when treating systemic infections (Wang *et al.*, 2025). In the same way, the successful clinical application of CRISPR-based antimicrobials, aptamer–antibiotic conjugates, and targeted nucleic acid therapies depends on developing delivery platforms that are not only selective and efficient but also manufacturable, biocompatible, and aligned with regulatory requirements (Mayorga-Ramos *et al.*, 2023).

4.9. Regulatory ambiguity and classification

Regulatory agencies frequently encounter challenges when attempting to classify hybrid antimicrobial therapies that blur the lines between drugs, biologics, and medical devices. For instance, a peptide–nanoparticle conjugate designed to deliver a CRISPR payload may fall into multiple regulatory categories, each with its own approval process. This fragmented framework can lead to delays in development, duplicate evaluations, and reduced investor confidence in novel therapeutic platforms. To address these issues and keep pace with rapidly advancing technologies, there is a clear need for more consistent classification criteria and the development of specialized regulatory pathways suited to multifunctional antimicrobial agents (Desai, 2012).

Many non-traditional antimicrobial agents rely on complex chemical synthesis or multi-step formulation processes that are not yet optimized for industrial-scale production (Onwuemelem *et al.*, 2025). The large-scale manufacturing of synthetic antimicrobial peptides (AMPs), metal–organic frameworks (MOFs), or RNA-based therapeutics under GMP-compliant conditions remains technically demanding and financially intensive (Folorunsho *et al.*, 2024). In the absence of well-defined market incentives or reimbursement strategies, biotechnology companies may be reluctant to invest in these candidates—even when supported by compelling preclinical data (Baindara, 2025).

4.9.1. Adaptive Resistance to Novel Strategies

Even therapies that are not directly lethal—such as quorum sensing inhibitors, biofilm disruptors, or metal-based approaches—are still subject to evolutionary pressure. Bacteria can adapt by rewiring their metabolism, modifying efflux systems, or acquiring genetic mutations. This highlights the critical need to include long-term resistance monitoring and surveillance as part of the development strategy for all new antimicrobial technologies. Successfully addressing these obstacles will depend on stronger coordination between laboratory research and clinical application, more adaptable regulatory frameworks, and enhanced collaboration across scientific, industrial, and healthcare sectors. Only through such integrated efforts can next-generation antimicrobial chemistries transition effectively from the research bench to clinical practice (Juszczuk-Kubiak, 2024).

4.9.2 . Future directions and outlook

Addressing the global threat of antimicrobial resistance (AMR) requires more than small advances—it calls for a fundamental

shift in how we understand, develop, and apply antimicrobial therapies. Rather than serving a supporting role, chemistry has become a central driver in this multidisciplinary effort. It enables the creation of smarter, more adaptable, and more resilient therapeutic platforms that are better equipped to meet the evolving challenges of AMR (Oseghale *et al.*, 2024). The future of antimicrobial development will rely on synergistic design, artificial intelligence, data-driven discovery, and personalized treatment strategies. It also requires a new perspective—one that views antimicrobials not just as fixed chemical entities, but as dynamic tools functioning within complex biological environments. Achieving this vision calls for ongoing collaboration among chemists, microbiologists, clinicians, data scientists, and policymakers. Only through such integrated efforts can we stay ahead of resistance and create meaningful solutions for global health (Dik *et al.*, 2017).

4.9.3. Rational combination therapies: Designing synergy at the molecular level

In the past, combination therapies were typically discovered through empirical methods that relied on pairing existing antibiotics based on trial and error. Today, synthetic chemistry enables the deliberate design of synergistic treatments starting at the molecular level. Scientists can now create hybrid compounds, such as antibiotic–efflux pump inhibitor conjugates or dual-action agents that target both bacterial membranes and internal pathways. These treatments are specifically engineered to exploit key weaknesses in drug-resistant bacteria. Newer approaches, including molecular logic gate systems that respond only to multiple microbial signals like quorum sensing molecules or pH fluctuations, demonstrate how precise chemical design can improve both selectivity and therapeutic effectiveness. Fully realizing these innovations will depend on the development of better tools for measuring synergy, as well as advanced screening platforms that consider resistance mechanisms from the very beginning (Si *et al.*, 2023).

4.9.4. AI and machine learning in antimicrobial design

Artificial intelligence (AI) and machine learning (ML) are rapidly reshaping the field of antimicrobial discovery (Lawal *et al.*, 2025). These technologies harness large-scale chemical datasets generated from high-throughput screening, DNA-encoded libraries, and omics-based profiling. Deep learning algorithms have shown growing success in predicting antimicrobial potency, safety profiles, and the likelihood of resistance development. Generative models are now capable of designing entirely new small molecules and antimicrobial peptides that operate through previously unknown mechanisms. As these technologies continue to evolve, the integration of explainable AI will become increasingly important. It will help researchers better understand structure and activity relationships, especially in complex systems such as metal-based therapeutics, supramolecular constructs, and dynamic covalent compounds (Green *et al.*, 2021).

4.9.5. Toward Personalized AMR Therapies

One of the most transformative trends in antimicrobial development is the move toward personalized treatment strategies. Advances in metagenomic sequencing, microbiome profiling, and rapid diagnostics have made it possible to identify pathogens in real time and to assess the broader microbial environment unique to each patient (Lawal *et al.*, 2025). This progress enables the development of therapies that can precisely target pathogenic bacteria while sparing beneficial microbes. Chemistry is central to this approach, supporting the creation of intelligent therapeutics that respond to biological cues such as inflammation signals, enzymatic activity, or oxygen concentration. These stimuli-responsive agents can be activated specifically at the site of infection, minimizing systemic exposure. In this evolving model, antimicrobial treatment will shift away from generalized solutions and toward tailored interventions that consider both the pathogen and the host biology (Olsen & Riber, 2025).

Bio-orthogonal Chemistry for In Situ Antimicrobial Activation

New developments in chemical biology are making it possible to use antibacterial methods with very precise control across time and space. Bioorthogonal processes, especially the tetrazine–trans-cyclooctene (TCO) system, together with photoactivatable chemicals and enzyme-sensitive linkers, make it possible to selectively activate antimicrobial drugs at the site of infection. These approaches change inactive precursors into pharmacologically active forms solely in sick tissues. This greatly lowers systemic exposure and off-target consequences. These kinds of precise methods are especially promising for treating infections that are hard to reach, like those caused by bacteria that form biofilms or pathogens that live inside cells. They are also useful for patients who are at risk of getting sick and need to limit damage to healthy tissue as much as possible (da Silva *et al.*, 2017).

4.10. Funding innovation: public–private collaborations

Successfully scaling next-generation antimicrobial strategies will require a fundamental shift in how innovation is financed and sustained. Traditional market-driven approaches have repeatedly failed to provide sufficient incentives for antibiotic development, even as the threat of antimicrobial resistance continues to escalate (Folorunsho *et al.*, 2025). The Global Antibiotic Research and Development Partnership (GARDP) and CARB-X are two public-private partnerships that are starting to fix this problem by paying for early-stage research and lowering the risks that come with high-potential candidates. But to make real progress, we need to develop funding systems that are more stable. Platforms that focus on chemistry, which often have specialized infrastructure, complicated regulations, and the need for collaboration across disciplines, are especially well-suited to benefit from integrated support models that bring together academic research, industrial capabilities, and government investment. Figure 3 shows the most important processes needed to take new chemical antibacterial discoveries from the lab to the clinic (Folorunsho, n.d.; Muteeb *et al.*, 2023).

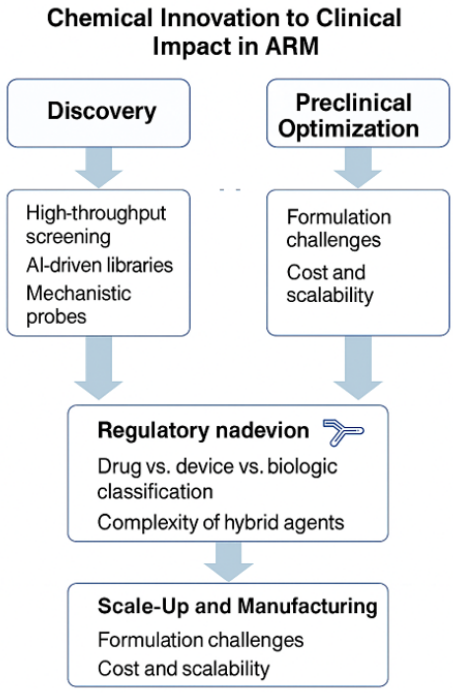

Figure 3. Translational Roadmap from Chemical Innovation to Clinical Impact in AMR Therapies

This diagram shows the main steps needed to move chemistry-based antimicrobial resistance (AMR) therapies from the first discovery to being used in clinical settings. Using high-throughput screening, machine learning–guided chemical libraries, and mechanistic probes that are meant to find new biological targets, the first step is to identify the compounds. In the preclinical phase, the main goals are to improve delivery platforms, molecular characteristics, pharmacokinetics, and early safety assessments. After that, there is a regulatory review, with a focus on agents that are complicated or have several functions and don't fit neatly into existing approved categories. The last step focuses on manufacturing issues, such as scalability, formulation stability, and the potential to make money. The roadmap shows the diverse and interconnected processes that need to be taken to turn cutting-edge chemical methods into treatments that work for AMR.

4.11. A call for integrative scientific convergence

The future of antimicrobial resistance (AMR) solutions will not be shaped by isolated advances or incremental progress. Instead, real advances will come from profound scientific convergence, which is when chemical biology works with materials science, microbiology, immunology, computational modeling, and systems pharmacology. This approach from several fields lays the groundwork for smart and sensitive medicines that can not only kill infections but also find microbial signals, change to resistance patterns, and grow in real time to deal with new threats (Ahmad *et al.*, 2025).

In the future, researchers need to work together in a way that really integrates all of their fields. For example, chemists, doctors, data scientists, and engineers should all work together from the beginning to create novel compounds, diagnostics, and delivery systems. Chemistry does a lot more than only give us analytical tools; it gives us the basic framework for fighting antimicrobial resistance. The biggest changes will come from new drugs that are precise, adaptable, and good for the environment. These drugs will not only build on old models. There are already a lot of tools available, and everyone knows how important the situation is. The way forward is apparent, and now is the time to act (Ekins *et al.*, 2014).

5. CONCLUSIONS

Thank you for the clarification. Here's a revised version of the Conclusion section, now enhanced with specific, actionable policy recommendations and community-based interventions grounded in the article's findings:

Antimicrobial resistance (AMR) is not an inevitable byproduct of evolution—it is a crisis accelerated by human behavior, pharmaceutical inertia, and regulatory gaps. This review establishes that chemistry is no longer a supporting discipline, but a driving force in reengineering how we fight infections. From targeted delivery platforms and gene-silencing technologies to smart materials and AI-assisted drug discovery, chemical innovation is transforming antimicrobial development into a precision science.

However, the successful translation of these advances from lab to clinic depends not only on scientific progress but also on strategic policy action and community engagement. To that end, we offer the following recommendations:

RECOMMENDATIONS

i. Establish a global fast-track regulatory framework for hybrid antimicrobial technologies—such as CRISPR-based agents, siderophore–antibiotic conjugates, and stimuli-responsive nanomaterials—ensuring that regulatory bottlenecks do not stall innovation.

ii. Implement reimbursement incentives for the development and responsible use of novel antimicrobials, including financial rewards for industry innovations that meet pre-set resistance mitigation benchmarks.

iii. Fund localized manufacturing initiatives to ensure equitable access to next-generation antimicrobials in low- and middle-income countries. Public–private partnerships should prioritize modular, GMP-compliant facilities that can adapt to produce complex chemical therapies.

iv. Mandate integration of AMR surveillance with digital prescribing platforms, allowing real-time resistance data to guide antibiotic selection at the point of care.

Community-Based Interventions

i. Launch national AMR literacy campaigns using culturally appropriate media, focusing on the dangers of antibiotic misuse and the importance of finishing prescribed treatments—even when symptoms resolve early.

ii. Train pharmacists and community health workers as antimicrobial stewards, equipping them with decision-support tools and empowering them to deny inappropriate antibiotic requests.

ii. Engage traditional leaders, educators, and faith-based organizations to co-deliver AMR education, especially in rural

and underserved communities where they are trusted sources of health advice.

iv. Support community-led environmental monitoring of AMR sources, such as agricultural runoff and hospital waste, using mobile-based citizen science platforms to report contamination and drive local policy change.

The path forward demands interdisciplinary cooperation—between chemists, clinicians, regulators, technologists, and the public. Only through such integrated, actionable strategies can we outpace resistance and secure a future where infectious diseases remain treatable. Chemistry holds the key—but only if it is unlocked in concert with informed policy and empowered communities.

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