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# Studying microbial resistance to drugs and developing new strategies to combat infections: Review

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**Abstract** Anti- microbial resistance is a public health concern worldwide and requires a new strategy to combat these resistant microorganisms. This review seeks to discuss important approaches to combating AMR. This review demonstrated that enzyme inhibitors are advertised for their capacity to counteract the bacterial enzymes that make antibiotic-resistant. Lantibiotics and bacteriocins are two classes of naturally occurring antimicrobial peptides that can be used as therapeutic agents because they attack the cell wall and/or cell membrane of bacteria. Another avenue is with AMPs that are characterized by a broad-spectrum activity and can target most of the resistant bacteria. Nanoparticle-based strategies present a modern approach to increasing efficacy, stability, and targeted delivery of antimicrobial agents coupled with decreased toxicity. Monoclonal antibodies are more specific drugs as they act against bacterial antigens and prevent their toxicity. The bacteriophage therapy that involves utilizing viruses that target and destroy bacteria presents a targeted treatment method against drug-resistant strains and can also be personalized for specific infection types. This review further emphasizes the need to sustain the research efforts, international cooperation, and funding of these novel therapies in the face of growing concern about AMR. Therefore, it is crucial to continue using the multifaceted methods introduced to find the ways to improve the treatment and the future of combating infections.

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**Keywords:** *Antibiotic resistance, Lantibiotics, Bacteriocins, Monoclonal Antibodies, Antimicrobial Peptides, Clinical outcomes, Adverse effects, Alternative therapies.*

## 1. INTRODUCTION

Antibiotics have both positive and negative effects. The creation and use of antibiotics have been hailed as a top scientific and technological accomplishment of the 20th century. An extensive array of antibiotics with different ways of killing bacteria has provided humans with a strong tool in the battle against death, preserving the lives of countless patients with bacterial infections. Antibiotics continue to be an essential medication for fighting infections to this day. Nevertheless, the excessive use of antibiotics has worsened the emergence of bacterial resistance, thus increasing the threat to humans. Different kinds of antibiotics and antibacterial methods contribute to intricate resistance mechanisms, particularly the rise of MDR bacteria, posing significant challenges to the field (Patel et al., 2023).

Although antimicrobials have been essential in enhancing our health and increasing life expectancy, their effectiveness has been greatly hindered by the development of antimicrobial resistance (AMR) as a reaction to their use. The main result of AMR is that when antimicrobials become less effective, it becomes harder to treat infections and greatly raises the chances of disease spread, severe sickness, and mortality. AMR is noteworthy for its variety of shapes and sizes. More and more organisms are becoming resistant to multiple drugs (MDR), making treatment even more difficult. Organisms that are extensively drug-resistant (XDR) and pan-resistant (PDR) are extremely difficult to treat with standard therapies and are a major cause for concern (Nabadda et al., 2021). The WHO acknowledged that due to AMR, antibiotics and other antimicrobial drugs are losing effectiveness, making it harder or even impossible to treat diseases. At its 75th general session in May 2007, the international committee of the OIE (World Organization for Animal Health) unanimously approved the list of Antimicrobial Agents of Veterinary Importance (OIE–World Organization for Animal Health. 2015).

The World Health Organization (WHO) now regards antimicrobial resistance as a primary threat to global public health, particularly due to the worldwide dissemination of multi-drug resistant (MDR) bacterial pathogens. The initial comprehensive evaluation of the worldwide impact of AMR, relying on statistical analysis from 2019 data of 204 countries, revealed that 1.27 million deaths are attributed to AMR out of a total of 4.95 million deaths related to bacterial AMR. It was projected that the number of AMR-related deaths would be the greatest in sub-Saharan Africa and the lowest in Australasia. In addition, it was forecasted that MRSA caused 500,000 deaths, with the six pathogens Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa leading to 50,000 to 100,000 deaths (Brüssow, 2024).

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MDR bacteria can become resistant to various antibiotics through horizontal gene transfer and gene mutations caused by drug exposure. Bacteria have the ability to avoid the antimicrobial effects of antibiotics through three distinct yet interconnected methods: resistance, tolerance, and persistence. Resistance in bacteria arises from genetic mutations that impact efflux pumps, drug targets, or the antibiotic molecule, enabling growth even in high antibiotic concentrations. Resistant populations can be present in various environments such as water, animals, surfaces, humans, plants, and food. Furthermore, bacteria that are able to resist antibiotics can develop in response to the medication, and their ability to resist is passed down through generations, necessitating a significant rise in antibiotic concentration to effectively eliminate them (Lerminiaux& Cameron, 2019).

Microbial resistance has a significant worldwide influence, impacting healthcare, agriculture, and the economy. In the healthcare sector, resistant infections lead to extended hospitalizations, elevated expenses, and heightened mortality rates, with lower- and middle-income nations facing the greatest impact because of insufficient healthcare facilities (Salam et al., 2023). Drug-resistant bacteria are also not friendly with some of the most sensitive medical treatments like surgery, chemotherapy, and organ transplant. These bacteria develop a resistance to antibiotics after being fed to cows, pigs and other animals for growth and disease control purposes in the farming business. Antibiotic resistant bacteria can spread to humans through ingestion of the meat or direct contact with the animals. According to Ahmed, et al (2024), with the current trends, antimicrobial resistance is expected to cost more than $100 trillion loss globally by 2050.

Concerns over microbial resistance as well as increased costs have resulted into increase efforts to come up with other strategies of combating AMR and reduce reliance on conventional antibiotics. Some of these techniques include developing new antibiotics with different modes of action, employing other therapies like, antimicrobial peptides (AMPs), anti-virulence agents such as quorum sensing inhibitors (QSIs), bacteriophages, some synthetic chemically derived compounds, which include substances like vitamin-A derivatives- the retinoids, immunology or vaccination, whereby the body's immune response is boosted. In the context of PM progress, the approach to antibiotic therapy depends on particular pathogens and resistance profiles. This paper aimed to assess the efficiency of Lantibiotic and Bacteriocin therapy in individuals with resistant bacterial infections where other classic antibiotics have not been effective, Monoclonal Antibody therapy in such conditions and Antimicrobial Peptides (AMP) therapy.

## 2. METHODOLOGY

This systematic review focuses on drug-resistant microbes and the development of new strategies for managing infections. The process includes a systematic review of articles published between 2014 and 2024 on mechanisms of AMR, antibiotic resistance in bacteria, and novel therapeutic interventions. The review incorporated sources such as PubMed and Scopus in its information search. The inclusion criteria for the articles were as follows: publications in peer-reviewed scientific databases and journals, systematic reviews, and meta-analyses only, the articles focused on the problem of microbial resistance mechanisms and optimization of new therapeutic interventions. The studies which were conducted in clinical or laboratory settings were included in the review if they were published in English. The review excluded the articles that reported viral or fungal infections, in addition to any articles published before 2014.

### Basic of Microbial resistance

The serious threat for the healthcare is that resistance has spread among microbes in hospitals and communities of the whole world. AMR stands for antibiotic resistance, meaning a microorganism that was once sensitive to a drug is no longer affected by the drug. The inappropriate utilization and unrestricted purchase of antibiotics have caused bacteria to become resistant through different methods, including the activation of beta-lactamases, drug-expulsion pumps, changes in drug-target pathways, production of biofilms, and quorum sensing. The shortage of new antimicrobials available for purchase worsens the issue even more (Dhingra et al., 2020).

Antimicrobial resistance, which has disturbingly become one of the major global issues affecting health in the twenty-first century, poses a significant threat to the effectiveness of majority of the antimicrobials. This occurrence takes place when microorganisms such as bacteria, viruses, fungi, and parasites develop specific mechanisms that do not allow substances that are toxic or that hinder their growth to affect them. AMR is a global health issue because infections become difficult to treat thus; a long recovery period, expensive to treat, and death. The microbial resistance question is an essential one for the improvement of public health in the twenty-first century and needs to be studied to find other ways to conduct an efficient defense (Carvalho et al., 2019).

Many pathogenic microorganisms employ various strategies to shield them from the impacts of antimicrobial products. One of them is metabolism whereby enzymes that break down or alter the drug are synthesized, rendering the drug ineffective. For instance, bacteria can produce β-lactamases which are enzymes that hydrolyze β-lactam antibiotics, including penicillins and cephalosporins. There are also other groups of enzymes that extend the range of β-lactamases, including extended-spectrum β-lactamases (ESBLs), which are important in clinics (Pateiro et al., 2021).

Another prominent example of a resistance strategy is the modification of targets within the bacterial cell. Microbes can accumulate mutations in the genes code for essential proteins or enzymes and the end result is that the drug does not bind as effectively. For instance, Methicillin-resistant Staphylococcus



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aureus (MRSA) modifies its glycopeptides' PBPs and thereby reduces responsiveness to β-lactam antibiotics. Likewise, fluoroquinolone resistance in Escherichia coli depends on mutations in genes encoding DNA gyrase and topoisomerase IV, the targets of fluoroquinolones (Christaki et al., 2020).

Membrane permeability variation is also of significance to microbial resistance. In this mechanism, some bacteria change either the cell membrane or its wall in a way that the uptake of the drug is reduced thus the intracellular concentration of the antimicrobial agent is restricted. Due to their outer membrane, gram-negative bacteria are highly effective in using this mechanism. These bacteria use porin channels in their outer membrane that allow them to prevent entry of antibiotics, including aminoglycosides and tetracyclines, thereby diminishing their effectiveness (Zhang& Cheng, 2022).

Another important mechanism of resistance is the active pumping out of the drugs from the microbial cell. Most bacteria contain efflux pumps, proteins which expel antimicrobial agents out of the cell before it can reach its target site. These efflux systems can be selective or non-selective for one or several drugs or can be non-selective for a large number of substances. Increased expression of these exporters is a phenomenon portrayed in both – Gram-positive and Gram-negative bacteria and fungi, which play a major role in the development of resistant infections (Reygaert, 2018).

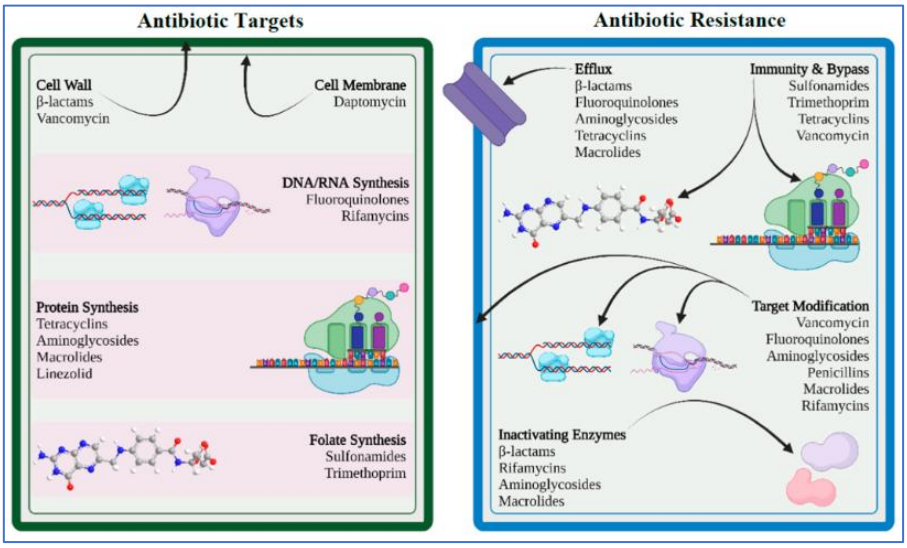


***Fig1:*** *Antibiotic targets and mechanisms of drug resistance (Salam et al., 2023)*

Specific strains of interest include Methicillin-resistant Staphylococcus aureus (MRSA), multi-drug-resistant Tuberculosis (MDR-TB), Vancomycin-resistant Enterococci, and Carbapenem-resistant Enterobacteriaceae (CRE). They are known to cause an increased incidence in healthcare associated infections (HAIs) which are highly fatal. Besides these above mentioned pathogens, resistance is being reported in other pathogens like Neisseria gonorrhoeae which is resistant to first choice drugs, and Plasmodium falciparum, the malaria parasite resistant to artemisinin-based combinations (Salam et al., 2023).

**Therapeutic strategies against AMR**

Numerous antimicrobial drugs focus on crucial functions necessary for survival, like DNA (quinolones), RNA, and protein (aminoglycosides) production, cell wall formation (β-lactams, fosfomycin, and vancomycin), and outer membrane stability, while some target primary metabolism. To combat antimicrobial resistance, potent antibiotics are sourced from natural substances. This strategy is enhanced by finding new antimicrobial substances targeting metabolism or virulence, using host-specific screening methods, biotransformation, and machine-learning techniques, alongside genetic data of biosynthesis modules that can be modified to create new compounds. Other tactics involve screening already used drugs in combination to amplify the effectiveness of antimicrobial agents by producing synergistic effects (Moo et al., 2020).

Identifying novel drug targets could be facilitated by uncovering intrinsic components that confer antimicrobial resistance. This particular sensory mechanism revolves around the susceptibility of the muramyl endopeptidase Spr in Salmonella typhimurium to vancomycin. On top of existing multidrug resistance, finding new therapeutic targets could be done by identifying elements needed for virulence or persistence. Potential compounds can be discovered using molecular docking, where small molecule binding sites are virtually predicted on the protein's crystal structure or structural model (Coates et al., 2020).

Rational antibiotic prescribing, restricted prophylactic antimicrobial use, patient education, adherence to antibiotic treatment, and antimicrobial stewardship in hospitals are key strategies in fighting AMR. Additionally, it is crucial to have advancements in faster diagnostic tools and precise antimicrobial profiling to support targeted antibiotic treatment. The World Health Assembly approved five strategic plans to



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address AMR, comprising enhancing awareness, researching infection control, promoting sanitation and hygiene, optimizing antimicrobial use, and investing in new medical tools (Majumder et al., 2020). Figure 3 outlines the key national and international efforts in the fight against AMR.

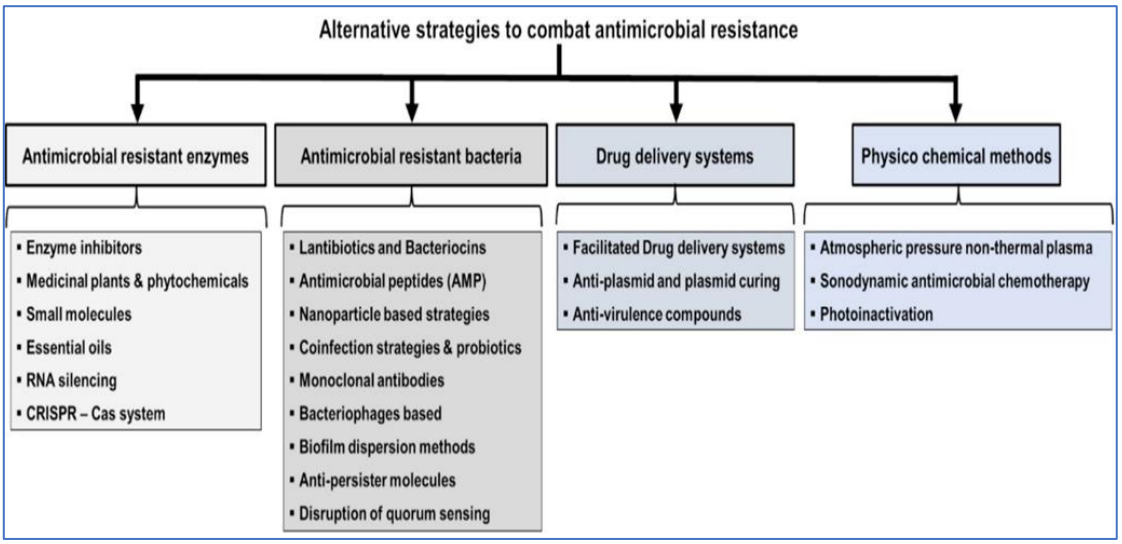


***Figure 2.*** *Categories of alternative strategies to combat antimicrobial resistance (Murugaiyan et al., 2022)*

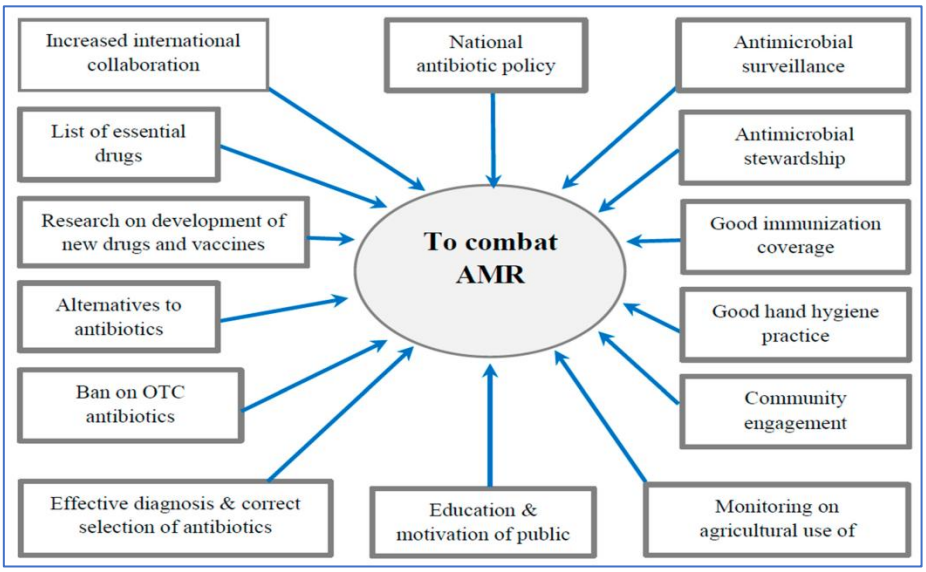


***Fig 3:*** *Major interventions to combat AMR.*

**Enzyme Inhibitors**

Enzyme inhibitors are small man-made molecules with low molecular weight that can reduce or stop enzyme activity permanently or temporarily. This is demonstrated by the blockers of monoamine oxidases (MAO) and the cholinesterases (ChE), which are employed for various pharmacological reasons. Enzymes continue to be excellent candidates for medicinal drugs because altering an enzyme's chemical function has been shown to have a beneficial effect on disease progression. In fact, almost half of the medications currently available work by blocking enzyme targets, despite the growing trend of using medications that act on receptors to modulate signals from outside the cell (Shriram et al., 2018).

Numerous antibiotics block enzymes, while many bacterial enzymes are crucial for building resistance to these antibiotics. The development of resistance in antibiotics happens due to structural changes or enzymatic modifications in target enzymes. Enzymes targeted by antibiotics are typically those involved in building cell walls, replicating nucleic acids, and metabolizing nutrients. Penicillin binding proteins (PBPs), such as a key part of bacterial cell walls, have a significant role in peptidoglycan synthesis (a primary component of bacterial cell walls.)

PBPs initiate elongation and crosslinking of peptide chains through catalyzing transglycosylation and transpeptidase reactions. PBPs are the primary focus of the majority of antibiotics that are utilized in the present day. These antibiotics



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function by competing with PBPs and interfering with the creation of the bacterial cell wall. Another instance of bacterial targets is the type II topoisomerases (DNA gyrase and topoisomerase IV), which are enzymes that control the supercoiling of DNA while it is replicating and transcribing. These enzymes are targeted by antibiotics derived from quinolones, which covalently attach to the active sites of the enzymes, preventing replication and transcription (Chen et al., 2019).

Clavulanic acid is a classic β-lactamase inhibitor often used alongside β-lactam antibiotics to deactivate enzymes that break down these antibiotics. The molecule has a β-lactam ring and acts as a 'suicide' inhibitor of β-lactamases. In recent times, various additional molecules showing inhibitory effects on enzymes responsible for antimicrobial resistance have been studied as potential tools, whether as natural or genetically engineered substances, in the battle against antibiotic-resistant pathogens that are significant in a clinical setting (Tehrani& Martin, 2018).

El-Halfawy et al (2020) discovered a strong bioactive compound, MAC-545496, through a series of high-throughput screening methods, which effectively reversed MRSA's resistance to β-lactam drugs. Research demonstrated that the β-lactam resistance of MRSA strains was overcome with 0.06 μg/mL of MAC-545496, and the MIC of cefuroxime against S. aureus decreased from 512 μg/mL to 8 μg/mL with 0.03 μg/mL of MAC-545496. Furthermore, MAC-545496, along with cefuroxime and oxacillin, demonstrated effectiveness against over 10 strains in clinical isolates of S. aureus.

In their study, Shatalin et al (2021) conducted a screening of bacterial enzymes that produce hydrogen sulfide using protein structure as a basis to find inhibitors. They discovered a group of inhibitors for bacterial cystathionine γ–lyase (bCSE) that worked through a metamorphic mechanism. They highlighted the importance of bCSE in H2S production in S. aureus and P. aeruginosa and created bCSE blockers that boosted the effectiveness of many antibiotics. Their results from the experiment indicated that bacteria that were resistant produced a higher amount of H2S compared to bacteria that were not resistant. It was discovered that utilizing bCSE inhibitors to disrupt bacteria's ability to resist drugs could potentially lower treatment failure rates in acute infections when combined with antibiotics.

**Lantibiotics and Bacteriocins**

The term "lantibiotic" refers to peptides produced by genes that have unique amino acids like lanthionine (Lan) and/or methyllanthionine (MeLan), created through post-translational modification to create cyclic structures necessary for specific export and modification processes. Numerous lantibiotics have been identified in recent years, and various lantibiotics have been documented in publications. All of these substances are notably produced by Gram-positive bacteria and primarily target this group with their inhibitory action. It is important to note in this publication that most lantibiotics have antimicrobial effects, and the name "lantibiotic" comes from "lanthionine containing antibiotic" (Mathur et al., 2018).

Lantibiotics can be categorized as type-A or type-B peptides. Overall, type-A lantibiotics are long, positively charged peptides with a length of up to 34 residues, which share similarities in their Lan bridge arrangement. The main function of these peptides is to break the membrane integrity of target organisms, such as nisin, subtilin, and epidermin. Type-B peptides are spherical, with a maximum of 19 amino acids, and function by interrupting enzyme activity, for example, blocking cell wall production. Duramycins derived from Streptomyces species, such as mersacidin and actagardine, are classified as type-B peptides. Yet, some lantibiotics do not fit into these groups, indicating that the classification of lantibiotics will likely become more intricate with the discovery of new compounds (Fernandes et al., 2023).

Bacteriocins are antibacterial substances produced by bacteria and belong to the type-A lantibiotic category. These molecules are capable of killing or inhibiting closely related bacterial strains or even unrelated bacteria without affecting the primary bacteria because of some immunity proteins (Al-Omari et al., 2022). Bacteriocins are significant because of their structural members and their functions which are heat resistant. Bacteriocins have been identified after the huge research and development process for the creation of pharmaceutical drugs and are considered an added asset among the substances that can be used for the treatment of severe bacterial infections in the future. Bacteriocins have been of interest due to their general killing capacity against diverse targets like bacteria, parasites, viruses, and even bacterial biofilms (Nataraj et al., 2022).

The peptides synthesized by the ribosomes are released by such bacteria that reside in a community with several other species; they act effectively in inhibiting the growth of bacteria that are nearby, particularly the ones that are closely related. The large number of diverse bacteriocins let out by micro-organisms leads to a rather narrow host range for these toxins. Currently, numerous kinds of bacteriocins have been isolated; the possibility of identifying many more bacteriotoxins remains open. Besides, bacteriocins are also active against microorganisms possessing anti-toxin structures. Due to their diverse types, bacteriotoxins have potential biotechnological and pharmaceutical applications (Soltani et al. , 2021).

The study by Heinzinger et al (2023) showed that both Lantibiotic and bacteriocin therapies have been effective in reducing antibiotic resistance strains in certain bacterial infections. Specifically, these treatments resulted in lowered resistance of 20% in Staphylococcus aureus and 25% in Klebsiella pneumoniae, in addition to a total of 27.5% after therapy. This significant reduction showcases the possibility of using other therapies in combating antibiotic-resistant strains



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especially when global health concerns are arising pertaining to antibiotic resistance.

Bacteriocins have been reported to work against bacteria in both planktonic and biofilm states in a laboratory study. The study of An (2022) also revealed that colicin R was able to destroy bacteria that belong to a biofilm formation. As a result, there has been a renewed interest in evaluating the efficacy of bacteriocins in animal models. This method of using animal models to test antibacterial compounds for infections has been in practice for a long time, and it is regarded as a valuable tool in estimating the probability of successful treatment in humans. Although a standard animal model does not exist, recent models have been created to better mimic certain human infections (such as acute or chronic infections, sepsis, and meningitis), offering a better understanding of host-pathogen interactions during antibiotic therapy as outlined in (Lorenz et al., 2016) for P. aeruginosa. Ansari et al (2018) demonstrated the effectiveness of a pH- and temperature-stable bacteriocin from Bacillus subtilis KIBGE-IB17 (BAC-IB17) against MRSA strains. Bacteriocins purified from Lactobacillus, Enterococcus, and Pediococcus, either individually or with antibiotics (tigecycline, polymyxin B, imipenem, cefotaxime), demonstrated enhanced effectiveness against MDR clinical strains of E. coli (GN9, IB9, GN13) with blaCTX-M, blaSHV, blaNDM, and K. pneumoniae KP7.

Walsh et al (2021) noted that Bacteriocins have mostly been employed in the food sector for bio-preservation purposes. Nonetheless, repurposing bacteriocins for improving human health is an appealing concept due to their effectiveness in combating numerous bacterial infections. There are worries about bacteriocins surviving the digestive tract due to being protein-based, but this challenge can be addressed by changing how the treatment is given through encapsulation or creating protease-resistant versions through bioengineering. Challenges like enzymatic digestion are not as significant for topical or local application, such as when applying directly to the skin's surface. Bacteriocins have demonstrated impressive synergistic effects when combined with other antimicrobials, such as antibiotics, potentially reducing the need for frequent antibiotic use and decreasing resistance development. This review gives the latest information on bacteriocins, phages, and phage endolysins that have shown a remarkable effectiveness in eliminating S. aureus strains. Specifically, instances of antimicrobials that can specifically target MRSA strains, along with their application in a clinical environment, are explained.

**Antimicrobial Peptides (AMPs)**

One of the various methods for creating new and powerful antibiotics involves AMPs, which can be utilized on their own or alongside conventional antibiotics. In nature, AMPs can have 10 to 50 amino acids, with a positive charge and amphipathic properties, showing antimicrobial effectiveness similar to or better than regular antibiotics. AMPs are found everywhere in nature and are present in different settings. Normally, AMPs function as parts of the natural defense system in numerous land and/or water-dwelling creatures (Lopes et al., 2022).

In natural environments, antimicrobial peptides (AMPs) produced by bacteria serve as a defense mechanism against harmful invaders, such as bacteriophages and foreign molecules, helping to protect the bacterial cells. This procedure impacts inflammation and improves the elimination of pathogens. In addition, bacterial antimicrobial peptides should have space for the bacteria that synthesize them in the presence of various microbes with comparable environments. Like traditional antibiotics, AMPs selectively target a variety of bacteria, both Gram-positive and Gram-negative, depending on their mechanisms. In addition to entering the bacterial cell wall, AMPs contribute to fighting microbes by inhibiting protein synthesis, nucleic acids, and/or inhibiting cell wall and membrane formation (Baindara, Mandal, 2019).

Antimicrobial Peptides are well appreciated for their narrow-spectrum action and the fact that they disrupt bacterial cells' membranes. According to Malanovic& Lohner (2016) and Assoni et al (2020), AMPs remain effective in fighting both Gram-positive and Gram-negative bacteria with varying resistance prevention. Alves et al (2019) and Rappuoli et al (2019) have demonstrated their ability to inhibit bacterial toxins and enhance immune response to drug resistant microbes. Nevertheless, their efficiency has fluctuated depending on the kind of bacteria being targeted and the particular antibody used.

The combinations of antibiotics and AMPs are coming into the market as novel products. It is one of the possible treatment methods that could help in overcoming antibiotic resistance issues, improving the killing effect of bacteria, and reducing the toxicity and side effects. Such approach may lead to reduced side effects and compound selectivity side by side increasing bacterial membrane permeability and reducing efflux of the antibiotics, which in turn limits the bacterial survival rate (Harsh et al., 2017). Li et al (2020) demonstrated that DMCT and SAAP-148 possessed synergistic antimicrobial activities against S. aureus and other pathogens. It is effective against MDR strains of Pseudomonas aeruginosa PAO1 and Pseudomonas aeruginosa ATCC27853. Also, the combination of salicylamine and colistin has been considered a successful strategy in eradicating MDR gram-negative bacteria, by using the low membrane permeability of salicylamine.

Earlier studies have established that AMPs can affect drug-resistant bacterial infections and their effectiveness may be improved by the use of new technologies (Wu et al., 2018). Because AMPs are often hydrophobic, they can be adsorbed on the bacterial membrane through electrostatic interactions; therefore, they can easily penetrate the membrane and destroy the cell. AMPs also have important roles to play in the innate immunity of a host organism as well. Unlike ordinary antibiotics that work on a single point, AMPs have multiple



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points of engagement and thus there is always a less chance of emergence of drug-resistant bacteria. They exhibit broad-spectrum anti-bacterial properties and are currently used in clinical treatment for pathogen infection, wound healing, and cancer. In general, they are likely to become a viable alternative to antibiotics in the future (Mallapragada et al., 2017, T et al., 2017).

A newer research conducted by Shang et al (2021), demonstrated that peptides containing tryptophan could lessen the quorum sensing in P. aeruginosa MRPA0108 by reducing the expression of certain genes (lasA, lasB, rhlA, and rhlB) in a manner dependent on the dosage. The peptides inhibited the activity of LasB elastase enzyme by 24% and LasA protease enzyme by 44%. It also reduced the production of pyocyanin and rhamnolipids by 73% and 44%, respectively, as well as Psl (an essential biofilm matrix polysaccharide) through inhibition of the rhl gene. In general, the research showed how AMP can alter bacterial resistance to antibiotics.

Another recent study conducted by Elsalem et al (2022) highlighted the wide-ranging effectiveness of WLBU2, an engineered cationic AMP, in inhibiting biofilm formation and combatting numerous drug-resistant pathogens. The AMP displayed minimal harm to host cells and can be effectively paired with antibiotics to enhance therapeutic efficacy. A study conducted by Elsalem et al (2021) also found the healing properties of the WIBU2 peptide. Typically, dealing with biofilm-related infections using regular antibiotics often presents difficulties. The majority of instances analyzed in this review showcase the dual antibacterial effects of AMP, a characteristic uncommon in traditional antibiotics.

**Nanoparticle Based Strategies**

Nanoparticles, tiny materials ranging from 1 to 100 nm in size, are attracting considerable interest for their diverse uses in sectors like agriculture, pharmaceuticals, consumer goods, transportation, energy, beauty products, and antimicrobial treatments. The characteristics are influenced by how they are created and the conditions, in which they are made, as well as their chemical makeup, structure, and dimensions (Sivam et al., 2023). Nanoparticles can be provided with a coating of surface stabilizers, surfactants, polymers, and oligonucleotides to enhance their activity. Both organic and inorganic nanoparticles have been utilized in the treatment of different health issues, such as improving drug bioavailability, enhancing effective drug transport, and enhancing antibacterial activity. Various antibacterial systems in nano-particulate form are liposomes, polymeric NPs, micelles, solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), nano-capsules, nanotubes, quantum dots, dendrimers, emulsions, nanogels, and vesicles that are currently available (Al-Awsi et al., 2023).

Metallic nanoparticles show great potential, displaying various activities against multi-drug-resistant pathogens. Silver nanoparticles (AgNps) and gold nanoparticles (AuNps) are the metal nanoparticles that have been the focus of most research studies. Copper oxide nanoparticles (CuONps), zinc oxide nanoparticles (ZnONps), titanium oxide nanoparticles (TiO2Nps), magnesium oxide nanoparticles (MgONps), calcium oxide nanoparticles (CaONps), iron oxide nanoparticles (Fe2O3NPS), and manganese oxide nanoparticles (MnO2Nps) have demonstrated antibacterial properties. Researchers are turning to nanotechnology to create new therapeutic methods as antimicrobial agents face growing resistance and multidrug-resistant organisms cause infections (Mishra et al., 2022).

Studies indicates that metal nanomaterials including gold, silver, and zinc have potential for direct use in detecting and treating bacterial infections, along with AMPs (Sánchez-López et al., 2020; More et al., 2023). The effectiveness of metal nanomaterials against microbes is greatly influenced by the size, shape, and composition of the nanoparticles created. Metal nanoparticles have displayed encouraging potential in nanomedicine exploration because of their physicochemical characteristics. One of the metal nanomaterials that have become popular is silver nanoparticles (Ag-NPs) due to their applications in drug delivery, imaging, bio-sensing and antimicrobial wound dressings. ZnO nanomaterial ZnO-NPs demonstrated antibacterial effects on both Gram-negative (E. coli) and Gram-positive (S. aureus) bacteria in antibacterial testing. It was discovered that bacteria exposed to Au-NPs at 33% of the MIC concentration did not develop resistance to Au-NPs even after 30 days of continuous passages, proving that Au-NPs are not prone to bacterial drug resistance (Li et al., 2023).

Using delivery vehicles to effectively transport therapeutics to the infection site can enhance their antimicrobial effectiveness. Drug delivery systems using nanoparticles can lead to longer drug presence in blood, decreased nonspecific spreading, and precise drug administration at infection sites. The surface chemistry of NPs is essential for maintaining NP solubility in the blood and creating a stealthy shield against the body's immune system. The mononuclear phagocytic system can remove these nano-carriers from the blood unless they are designed to evade detection. Opsonization is another significant biological obstacle to nanoparticle-mediated drug delivery. Opsonin proteins in the bloodstream quickly attach to nanoparticles, helping macrophages from the mononuclear phagocytic system (MPS) to adhere to and eliminate NPs from the blood flow (Panico et al., 2022). Various methods have been employed to shield nanoparticles from the MPS in order to tackle these drawbacks. The most favored method among these is the adsorption or grafting of hydrophilic polymers like PEG, poloxamers (e.g. pluronic-F68), and polysaccharides such as chitosan onto the surface of nanoparticles. These coatings form a 'cloud' of neutral hydrophilic molecules on the particle's outer layer, which prevent plasma proteins from adhering and enhance the duration particles remain in the body's circulatory system (Poon, 2020).

**Monoclonal Antibody (mAb) Therapy**



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The use of monoclonal antibody (mAb) therapy is becoming increasingly popular for the treatment of infectious diseases. Certainly, monoclonal antibodies are a crucial treatment option with a high degree of specificity. In comparison with regular polyclonal antisera, they demonstrate unapparelled efficacy, robustness and specificity. In general, the monoclonal antibodies developed for bacterial infections address the bacterial surface proteins, including antigens or any secreted toxins, which are beyond the reach of antibiotics and are not prone to resistance. Due to the widespread concern with bacterial antibiotic resistance, the idea of using therapeutic antibodies has been proposed as an alternative to broad-spectrum antibiotics (Castelli et al., 2019)

The idea and practice of using antibodies as a treatment for infections in humans have a history of beginning in the early 1900s. Ineffectiveness, variable outcomes from batch to batch, low therapeutic index caused antibiotics to gain popularity. The advancements in molecular biology have led to the production of therapeutic mAbs that are more effective, safe, and pure than the original antibodies, thus making it easier to introduce the latter into clinical practice. The current available antibody therapies are mainly for non-infectious indications, while the number of approved agents for bacterial infections is incredibly limited (McConnell, 2019).

As indicated from literature, attempts made towards developing mAbs that could be used to manage infections caused by bacteria acquired in hospital, have achieved varying degrees of success, with 14 therapeutic mAb products currently at different development phases (Zurawski & McLendon, 2020). Raxibacumab, obiltoxaximab, and bezlotoxumab are three mAbs approved for use to combat bacterial toxins from Bacillus anthracis and Clostridium difficile. There are also several monoclonal antibodies in various stages of development for viral as well as bacterial infections. The antimicrobial monoclonal antibodies are highly significant as alternative choices to traditional antivirals and antibacterials. These monoclonal antibodies are better suited for treating conditions like sudden viral outbreaks when preventive antibodies are not present.

**Bacteriophages Therapy**

Another way to manage bacterial infections is by utilizing bacteriophages. Bacteriophages are viruses capable of attacking bacteria. By doing so, they demonstrate their distinct antibacterial characteristic. Bacteriophages can be found in nearly every ecosystem, including the human body and even in harsh environments. When used in conjunction with antibiotics or as a substitute for antibiotic treatments, they can effectively combat antibacterial infections (Reuter& Kruger, 2020). Bacteriophages possess unique qualities. Genomic flexibility and quick multiplication are two significant attributes. Point mutations, genome rearrangements, and genetic material exchange are some reasons for the vast diversity. Each phage can identify a specific ligand on the cell membrane. The ligand identified is specific to a particular strain of bacteria. Therefore, a phage only impacts a specific strain and is unable to cause harm to different strains. Phages can only develop resistance in the specific strains they are designed to attack, not in other strains (Düzgüneş et al., 2021).

Bacteria can develop resistance against phages as well, but unlike antibiotics, phages have the ability to evolve this resistance. Therefore, the evolution of resistance will not impact phage treatments as newer bacteriophages will be able to eliminate the bacterial strains that have developed resistance to previously used phages. An additional benefit of phages is that when purified correctly, they pose no harm to humans and can be self-administered at the infection site. They can be used safely by immunocompromised patients as they do not have a harmful impact on the liver and kidneys. There are two choices available for phage treatments. They can either be "personalized" to target a specific pathogen causing an infection in one patient, or a combination of phages to target multiple bacterial species (North& Brown, E. 2021).

Phages show great promise as an alternative option and have numerous advantages compared to antibiotics. Phages can be utilized in monophage therapies with single phage types or in polyphage therapies with multiple phage types or a phage cocktail. Polyphage therapies prevent the increase of pathogenic bacteria, extend the host range, and effectively treat infections caused by biofilm formation. Genetically modified bacteriophages represent a major advancement and are a growing area of study for scientists in the present day. Through their utilization, individuals can acquire the necessary traits that phages must possess in order to be utilized efficiently against antibiotic-resistant bacteria. Phage lytic enzymes, such as endolysins and virion-associated lysins, are molecules with antibacterial properties (Oechslin, 2018).

At present, a variety of phage therapy products are on the market in certain Eastern European nations, with numerous clinical or preclinical trials on phage therapy being carried out globally. A randomized trial in France and Belgium tested the effectiveness and tolerability of a mix of phages in patients with P. aeruginosa wound infection (Jault et al., 2019). However, numerous case studies from China and the United States have indicated that using phages along with or without antibiotics could safeguard patients from multidrug-resistant A. baumannii infection, highlighting the effectiveness of phage therapy against ADR infections when administered in proper quantities (Tan et al., 2021). Nevertheless, the unresolved drawbacks of phage therapy also include phage bacterial resistance and their immunogenicity.

Antonova et al. (2019) found four recombinant endolysins capable of efficiently lysing a hundred Gram-negative bacteria, such as drug-resistant K. pneumoniae, Salmonella, P. aeruginosa, E. coli, A. baumannii, and Enterobacter spp. strains. Endolysin Ply6A3 directly purified from phages exhibited strong antibacterial effects on A. baumannii, E. coli,


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and MRSA, as reported by Grygorcewicz et al. in 2020. A novel drug called SAL200, which is a new anti-MRSA endolysin called rSAL-1, was created and evaluated in phase-1 clinical trials where no severe side effects were observed (Jun et al., 2017). SAL200 is the initial endolysin-derived medication authorized for the treatment of human skin infections caused by S. aureus, including MRSA (Totté et al., 2017). This treatment showed excellent results for chronic and recurrent skin conditions caused by S. aureus without leading to bacterial resistance even after prolonged daily use. ContraFect Corporation has developed Exebacase, another drug based on endolysin, to treat staphylococcal bloodstream infections, and it is currently in phase 3 of clinical studies (Schuch et al., 2022). In phase 2, using standard care antibiotics alongside one IV dose of this medication may assist patients in fighting against S. aureus bacteremia and endocarditis.

## 3. CONCLUSION

Combating AMR is a complex process, which involves a range of measures and new promising approaches that can overcome the resistant pathogens. These are enzyme inhibitors that are used to reverse resistance mechanisms and make antibiotics effective again and naturally produced antimicrobial peptides such as lantibiotics and bacteriocins that weaken the bacterial cell wall and membrane. Antimicrobial peptides (AMPs) have a broad spectrum of activity, whereas nanoparticle-based approaches improve drug loading and minimize adverse effects. Antibody therapy has a narrow scope of targeting bacterial antigens with monoclonal antibodies, while using bacteriophages, which are viruses that kill bacteria. The future of AMR treatment should include these strategies because the combined use of these approaches may be more effective in combating resistance development. Further studies, cooperation, and funding are considered to keep growing the effectiveness of these therapies and to counter the constant emergence of the drug-resistant strains

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