IJPSR (2025), Volume 16, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 March 2025; received in revised form, 23 April 2025; accepted, 26 April 2025; published 01 October 2025

ADDRESSING THE GLOBAL THREAT OF ANTIMICROBIAL RESISTANCE: EMERGING APPROACHES, INNOVATIONS, AND RETHINKING STRATEGIES FOR FUTURE CONTROL

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Keywords:

Antimicrobial Resistance (AMR), Quorum Sensing Inhibitors (QSI), Monoclonal antibodies, Antimicrobial Peptides, Nano particles

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ABSTRACT: Antimicrobials are vital agents that combat dangerous microorganisms, but increasing resistance to these drugs is a major challenge to global health security. AMR occurs when the intended killing drugs lose their effectiveness because pathogens have learned how to adapt and become resistant to them mainly as a result of overusing, misusing or using antibiotics in ways that are not suitable. Adhering with this pressing matter necessitates fresh methods coupled with an all-inclusive perspective. Literature was searched through indexed databases including Scopus, PubMed, Google Scholar and Science director. Research on novel AMR treatments is continuing. Anti-virulent therapy targets bacteria's virulence factors rather than eradicating them, preventing antibiotic-resistant strains. Naturally occurring or manufactured antimicrobial peptides have diverse modes of action and little resistance risk. Using antimicrobials to prevent infections reduces the need for curative antibiotics. Bacteriophage therapy employs viruses that infect and kill bacteria to treat illnesses. Plant derivatives like phytochemicals and nanoparticles are antimicrobial.Review addressing the challenge of antimicrobial resistance requirements and for multi-pronged approach, including surveillance, stewardship and development of new treatments. By implementing these approaches and fostering collaboration, current review focused on work towards sustainable solutions to protect public health and the utility of antimicrobial treatments. The time for action is now in order to mitigate the risk posed by AMR and ensure that our current arsenal of antimicrobials remains viable for future generations.

INTRODUCTION: The worldwide escalation of bacterial resistance to conventional medical antibiotics is a serious concern for modern medicine [1]. Each year, more than 2.8 million illnesses in the US are resistant to antibiotics. More than 35,000 people die as a result, according to CDC's 2019 Antibiotic Resistance (AR) threats report. Antimicrobial resistance may have an impact on individuals at every stage of life, as well as on the medical, veterinary, and agricultural sectors.

This makes it one of the most important public health issues in the entire world due to the fact that repeated drug administration and greater doses are common now a days. Antibiotic resistance has emerged against various types of antibiotics commonly used against harmful bacteria [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(10).2670-69

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(10).2670-69

Therefore, there is an immediate need to develop new approaches to handle this problem. Antibiotic resistance can be overcome only by understanding its mechanisms [1]. Major routes of antibiotic resistance include the efflux of antibiotic from the bacterial cell through efflux pumps, enzymatic modification or degradation of the antibiotic molecule, and alteration of the antibiotic target, which prevents binding of the antibiotic and, therefore, leads loss of its activity [1]. The mechanisms shown in **Fig. 1** are different approaches to bacterial resistance.

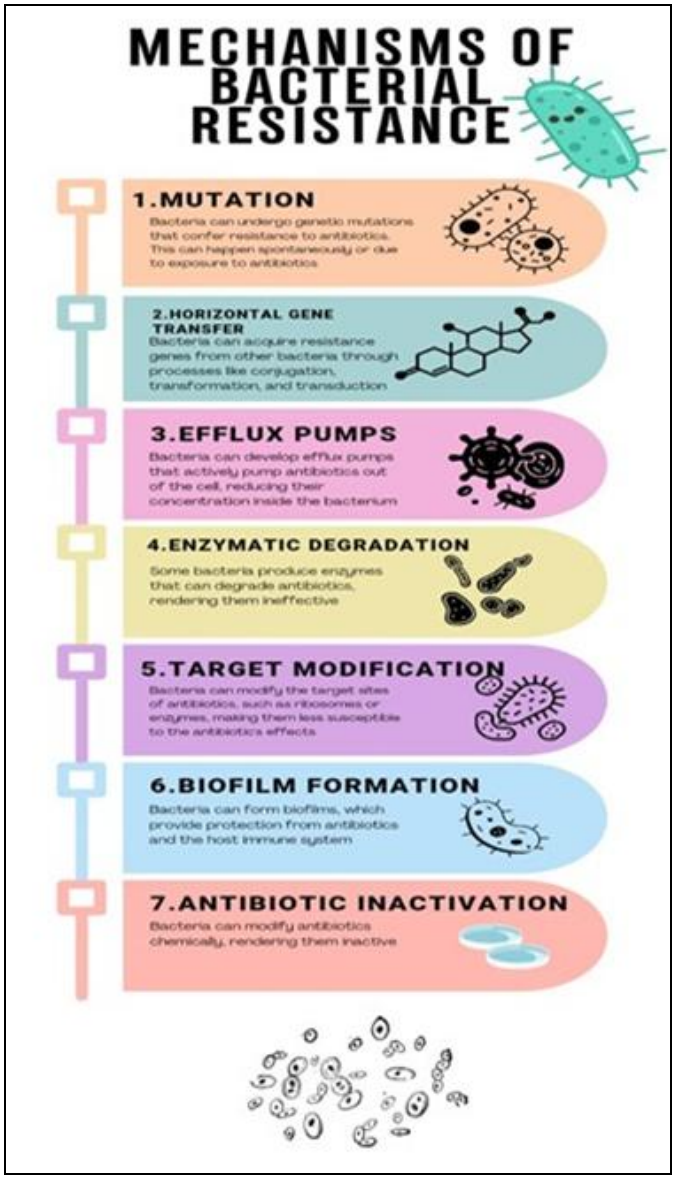

FIG. 1: DIFFERENT APPROACHES TO BACTERIAL RESISTANCE

METHODS: The literature was gathered from reputable databases including Scopus, PubMed, Elsevier, Science Direct, and NCBI journals. The selection criteria for journals primarily focus on Multidrug resistance microbial infections. Many papers have focused on the widespread occurrence of a significant infectious disease in the global population. The data was collected from 70 studies that focused on various aspects including epidemiology, medication resistance, patho-physiology, mechanisms of bacterial resistance, pharmacological therapy, and recurrence. The studies also explored new approaches to combat resistance. Microbiology and Immunology, General microbiology, microbial diversity, Scopus, and Web of Science were searched in the literature databases. **Fig. 2** representing the bibliometric analysis conducted in accordance with the PRISM criteria.

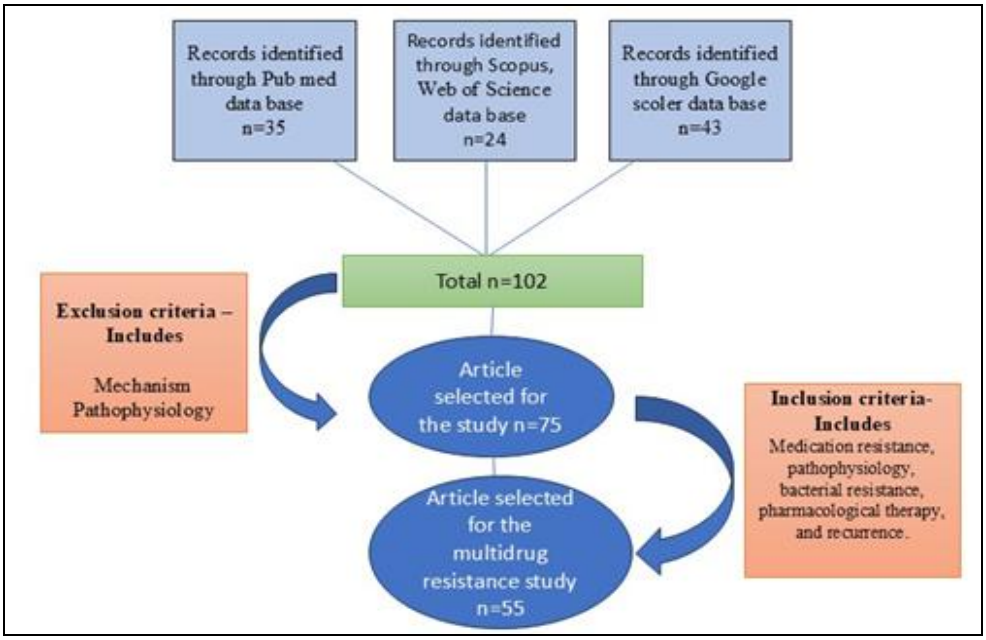

FIG. 2: REPRESENTING THE BIBLIOMETRIC ANALYSIS CONDUCTED IN ACCORDANCE WITH THE PRISM CRITERIA

DISCUSSION:

New Emerging Methods to Combat Resistance:

Nanoparticles: Nanoparticles (NPs) represent a promising frontier in combating bacterial resistance due to their unique properties and diverse applications in medicine. Allahverdiyev AM *et al*, have stated that metallic NPs [1], such as silver, zinc oxide, titanium dioxide, copper, and gold, have garnered significant attention for their potent antibacterial effects. Their small size and large surface area enable enhanced interactions with bacterial cells, disrupting vital functions like membrane integrity, respiration, and genetic material, thereby mitigating resistance mechanisms that bacteria may develop against traditional antibiotics [1] Shown in **Fig. 3** and **4**. Silver nanoparticles, for instance, have been combined with antibiotics like amoxicillin to significantly enhance their efficacy against E. coli. Similarly, titanium dioxide NPs exhibit photo-dependent antibacterial action by generating free radicals that disrupt bacterial membranes and cellular components, improving the effectiveness of penicillin's and other antibiotics against *Staphylococcus aureus* [2].

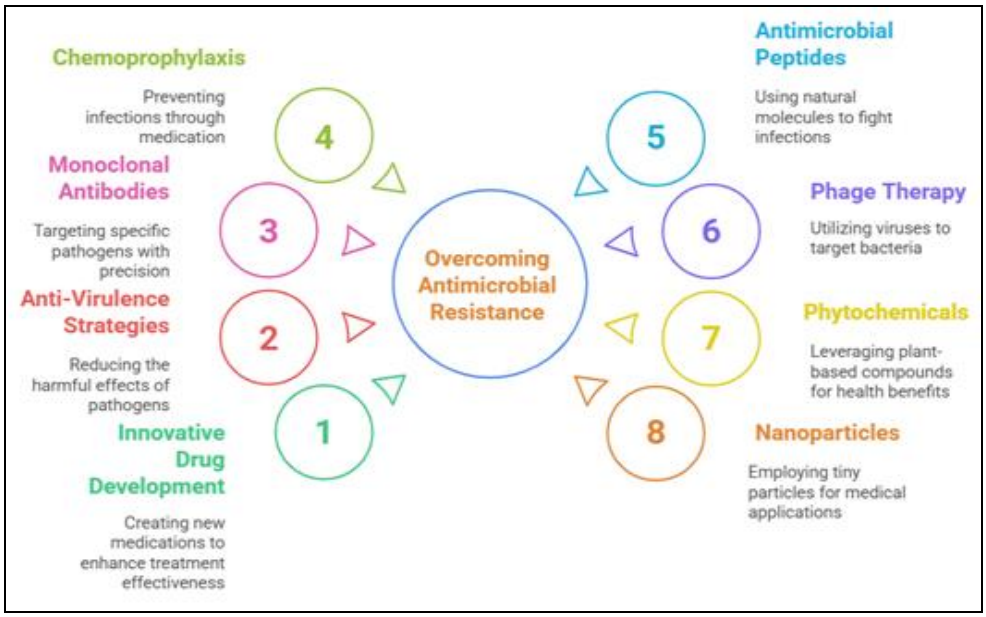

FIG. 3: STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE

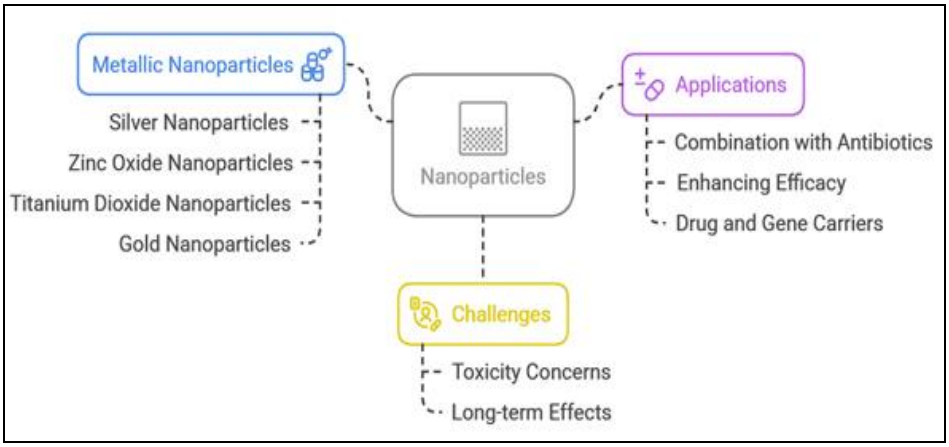

FIG. 4: NANOPARTICLES IN COMBATING BACTERIA RESISTANCE

TABEL 1: NEW EMERGING TRENDS TO COMBAT ANTIMICROBIAL RESISTANCE

New Methods	Mechanism of Action	New Emerging Trends
Nanoparticles	Disrupts bacterial cell membrane, generate ros, interference with bacterial metabolic process and biofilm formation, cell death	Nanoparticle enhanced antibiotics, combination therapies, antimicrobial nanoparticles, targeted delivery systems [1].
Antimicrobial Peptides	Peptides are typically positively charged and possess both hydrophobic and hydrophilic sides, which allow the molecule to permeate lipid-rich membranes and be soluble in aqueous settings. the peptide employs a variety of methods to kill target cells once it has penetrated into microbial membrane.	Topical applications, innate immune defencee [9, 10].
Chemoprophylaxis	Act in the bloodstream when the parasites invade the red blood cells.	Usage of rifampin, use of supreme preventive agents [19, 20].
Phage Therapy	Phage therapy uses viruses called bacteriophages to infect and kill specific bacteria. phages bind to bacteria, inject their DNA, replicate inside, and cause the bacteria to burst, releasing new phages. This method is effective against antibiotic-resistant bacteria and can disrupt biofilms.	Emerging trends in phage therapy involve enhanced phages through genetic engineering, using phage cocktails and enzymes to target biofilms, combining phages with antibiotics, personalizing treatments, and improved regulatory support [52].
Phytochemicals	Phytochemicals combat antibiotic-resistant bacteria by directly inhibiting bacterial growth, enhancing antibiotic efficacy, disrupting biofilms, modulating resistance mechanisms, and reducing inflammation.	Emerging trends in phytochemicals include advanced extraction techniques, synthetic biology for efficient production, targeted delivery systems, personalized nutrition, phytochemical-based drug development, and sustainable practices [55].
Anti-Virulence	Anti-virulence act by targeting bacterial virulence factors bacteria utilize quorum sensing, a cell-cell communication quorum sensing inhibitors (QSIS) disrupt this process.	Disrupting biofilm formation, inhibiting quorum sensing and neutralizing bacterial toxins [23].
Passive Immunization.	Monoclonal antibodies can directly or indirectly neutralize the toxins inhibit virulence factors and stimulate the host immune system.	IGy antibodies derived from chicken eggs are emerging as a promising alternative to overcome AMR [43]

TABLE 2: BIOLOGICAL SOURCE OF PHYTOCHEMICALS AND ITS TARGETING BACTERIA

Biological Source	Extract	Target Bacteria	Attributing Factors
Reserpine	*Rauwolfia, serpentina*	*Streptococcus spp.*	Anti-hypertensive and Anti-psychotic.
Berberine	*Berberi's species*	*E. Coli*	Anti-microbial and anti-inflammatory
Myricetum	*Vaccinium oxycoccus*.	*E. Coli*	Anti-inflammatory and anti-oxidant
Taxifolin	*Allium cepa*	*Enterococcus faecalis*	Antioxidant
Baicelem	*Scutellaria biacaleris*	*Methicillin resistance*	Antioxidant and Anti inflammatory
Geraniol	*Cynbopogon cutratus*	*Enterococcus aerogenes*	Insect repellant, antioxidant and anti-inflammatory
Osthole	*Pragos hulleri*	*B. subtiles*	Anti-oxidant and anti-inflammatory [55].

Zinc oxide NPs have shown synergistic effects with antibiotics such as ciprofloxacin against both *Staphylococcus aureus* and *Escherichia coli*, highlighting their potential in combination therapies. Gold nanoparticles, on the other hand, serve not only as carriers for drugs and genes but also enhance light-induced antimicrobial activity when paired with photosensitive compounds like methylene blue [1]. Transition-metal dichalcogenide NPs and other emerging nanomaterials are also being explored for their antimicrobial properties, suggesting a broadening spectrum of applications in antimicrobial therapy[4].Despite their promise, the use of NPs in clinical settings is limited by concerns over their potential toxicity and long-term effects on human health. The interaction of NPs with body tissues and cells varies based on their physicochemical properties, exposure route, dose, and duration, necessitating thorough evaluation before widespread clinical adoption [5]. Metallic nanoparticles present a multifaceted approach to tackling bacterial resistance, offering new avenues for enhancing the effectiveness of existing antibiotics and potentially developing novel therapeutic strategies. However, their safety profile must be rigorously assessed to ensure their viability in clinical practice [7].

Anti-microbial Peptides: AMP, also known as gramicidin. It has been discovered that gramicidin works well as a topical wound and ulcer therapy. Tyrocidine, a further AMP, was discovered in 1941 and demonstrated efficacy against both Gram-positive and Gram-negative bacteria [6]. Tyrocidine, however, was harmful to human blood cells. Another AMP was identified from a plant called Triticumaestivum that same year. This AMP was subsequently given the name purothionin and was discovered to be effective against some pathogenic bacteria and fungus. Prokaryotes, such as bacteria, and eukaryotes, such as protozoa, fungi, plants, insects, and animals, are both sources of natural AMPs. Animal tissues and organs exposed to airborne pathogens are primarily home to AMPs, which are thought to be the initial line of defense for the innate immune system against bacteria, fungi, and viruses. Therefore, AMPs are crucial in preventing the majority of infections before they manifest any symptoms [8, 9]. Small molecular weight proteins with broad range antibacterial activity against bacteria, viruses, and fungus are known as antimicrobial peptides, or AMPs. These evolutionarily conserved peptides are typically positively charged and possess both hydrophobic and hydrophilic sides, which allow the molecule to permeate lipid-rich membranes and be soluble in aqueous settings. The peptide employs a variety of methods to kill target cells once it has penetrated into microbial membrane [10]. AMPs attach themselves electrostatically to bacterial membranes in order to either rupture the membrane or penetrate the bacterium to impede intracellular activity [11]. Antibacterial peptides of the cathelicidin family are mainly used in anti-inflammatory, anti-infective and antifungal drugs and has good development prospects in the local treatment of diseases such as dermatitis and invasive burns. Histatins are a family of histidine-rich AMPs [13].

Cell wall Inhibitory Peptides: FDA-approved AMPs are bacterial cell wall synthesis inhibitors: vancomycin, oritavancin, dalbavancin, and telavancin. These glycopeptides bind to D-alanyl-D-alanyl amino acids in peptidoglycan chains and prevent the addition of N-acetylmuramic acid and N-acetylglucosamine. Their binding prevents peptidoglycan elongation and formation of cell walls, killing the bacteria [15, 16]. The number of AMPs in nature is large (the Antimicrobial Peptide Database contains 1700 unique peptides and the sequence diversity is high). They are usually about 30 residues long and usually cationic (+2 to+9). They have an average of 40-50% hydrophobic residues arranged so that the folded peptide acquires an amphipathic structure [17]. A variety of AMPs have been isolated from species in all kingdoms and classified based on their structure and amino acid motifs [18].

Chemoprophylaxis: Chemoprophylaxis involves the administration of non-vaccine pharmaceuticals to individuals who are not known to be infected to prevent potential infections and mitigate the health impacts and disease outcomes associated with such infections. The Advisory Committee on Immunization Practices recommends rifampin for prevention of meningococcal disease, administration of this drug is associated with failures and side effects and cannot be used during pregnancy [19]. Malaria chemoprophylaxis prevents the occurrence of the symptoms of malaria. None of the available drugs can kill the sporozoites

(inoculated by the Anopheles mosquito), which remain in the bloodstream for only a short time before reaching the liver. Medicines that affect the parasite in the liver tissue are called "siprophylaxis agents". Such as atovaquone and proguanil. Doxycycline has only a weak causal effect. Supreme preventive agents or blood schizontocidal drugs act in the bloodstream when the parasites invade the red blood cells. Most antimalarial drugs, such as mefloquine and doxycycline, fall into this category [20]. Pertussis may cause severe illness in young infants and result in complications such as apnea, cyanosis, feeding difficulties, pneumonia, and encephalopathy. Although ampicillin and amoxicillin have satisfactory *in-vitro* activity against *Bordetella pertussis*, they were found to be ineffective *in-vivo* in eliminating *B. pertussis* from the nasopharynx [21].

Since invasive fungal infection remains a common problem in the treatment of cancer patients, chemoprophylaxis of these opportunistic infections is urgently needed [22]. In patients with TBI causing intracranial hemorrhage, VTE chemoprophylaxis is warranted in patients with stable repeat computed tomography [23]. Chemoprophylaxis has no proven benefit in plastic surgery. Risk sharing is inefficient. A SAFE alternative to chemoprophylaxis is available that not only avoids additional risk but also increases patient safety. The plastic surgeon's choice is not between venous thromboembolism and hematoma. The choice is between thromboembolism and adjustment of anesthetic and surgical practices to reduce the risk to baseline[24]. The most commonly prescribed antimalarial chemoprophylaxis was atovaquone/ proguanil. Mefloquine was sometimes prescribed to patients with other comorbidities listed as contraindications, but most physicians noted contraindications. Mefloquine was often prescribed to children and pregnant women [25].

The use of antibiotics in the prevention of dental bacteremia, infective endocarditis, infections in patients with hip and other joint prostheses, and infections after dental surgical procedures is discussed [26]. Wound infections are a significant complication after major oncological head and neck surgery. Because of the controversies associated with the use of chemoprophylaxis, a controlled trial was designed. Intravenous Augmentin (amoxicillin and clavulanic acid) significantly reduces the incidence of postoperative sepsis [27].

Anti-Virulence (QSIs): The rise of multidrug-resistant pathogens poses a grave global healthcare challenge, with predictions suggesting higher mortality rates from infections than cancer by 2050 if current trends persist. Microorganisms employ diverse resistance mechanisms against antibiotics, underscoring the urgency for novel antimicrobial discoveries. Anti-virulence therapy offers a promising strategy by targeting bacterial virulence factors that contribute to pathogenicity. Bacteria utilize quorum sensing, a cell-cell communication system involving autoinducers, to regulate virulence factor production. Quorum sensing inhibitors (QSIs) disrupt this process, potentially reducing the need for broad-spectrum antimicrobials and mitigating resistance. The prevalence of multidrug-resistant ESKAPE pathogens[28]further underscores the critical need for innovative approaches to combat bacterial infections effectively, emphasizing the importance of identifying new treatment strategies against virulence factors crucial for microbial pathogenesis .These factors are often classified in three forms, including membrane associated, secretory or cytosolic [29].

Blocking the activities of virulence factors is a new approach that has emerged over the last decade. Anti- virulence drugs, the new class of drugs, target virulence factors of pathogens instead of killing or stopping their growth and consequently disarm infectious pathogens. Anti-virulence drugs interfere with the interaction of the pathogen with its host, and thereby reduce damage to the host and impair the organism’s ability to cause disease without killing it or creating selective pressure[30].Research on the inactivation of diphtheria and tetanus toxins are the first examples of the anti-virulence approach [31, 32]. Also, bezlotoxumab is the first anti-virulence agent approved by the US food and drug administration (FDA). This agent blocks TcdB in *Clostridioides difficile* [33]. There are a variety of bacterial targets for anti-virulence therapy, however some of the most attractive targets are adhesins, toxins, bacterial communication, two component systems and non-coding RNAs. Studies in recent years have suggested a variety of compounds as candidates for anti-virulence therapies.

Several substances have demonstrated inhibitory activity against quorum sensing (QS) and virulence factors in *Staphylococcus aureus* and *methicillin-resistant Staphylococcus aureus* (MRSA). Chalcone and Sclareol both exhibit anti-QS properties in *S. aureus*, leading to downregulation of hla and agrA expression [34], as well as reduced hemolysin production. Azan-7 inhibits the Agar quorum sensing signaling specifically in MRSA [35]. Staquorsin downregulates RNA transcript levels in *S. aureus* [36], contributing to its anti-QS effects. Dracorhodin perchlorate reduces hemolysis and suppresses hla and agrA expression in *S. aureus* [37]. Peptidomimetics also target the Agr system activity and quorum sensing in S. aureus, highlighting their potential as inhibitors of virulence factors in these bacterial pathogens [39].

Bacterial quorum sensing (QS) is a vital mechanism where cells respond to population density through gene regulation, crucial for survival and competitiveness. QS utilizes signaling molecules, or autoinducers facilitating chemical communication [40]. Gram-positive bacteria employ a two-component system with sensor kinase receptors and cytoplasmic transcription factors regulating gene expression via phosphorylation. In contrast, Gram-negative bacteria like Pseudomonas, Acinetobacter, and Burkholderia use acyl-homoserine lactones (AHLs) as autoinducers, binding to regulatory proteins and influencing enzyme and virulence factor secretion genes [41].

QS influences virulence traits, making it a target for combating antibiotic resistance through quorum quenching (QQ), which obstructs signaling. QQ methods include inhibiting, mimicking, degrading, or modifying QS signals. Nanotechnology, particularly selenium nanoparticles (SeNPs), enhances delivery of anti-virulence compounds like honey polyphenols, known for anti-QS activity against *P. aeruginosa*. Integrating nanotechnology with anti-virulence therapy holds promise in disease treatment by confronting pathogenic infections effectively [42].

Passive Immunization: Passive immunization is one of the best and safest way to combat resistance from the antibiotic resistance. Mono clonal antibodies are the possible way for passive immunization. The mechanism of the monoclonal antibodies can directly or indirectly neutralize the toxins inhibit virulence factors and stimulate the host immune system. These functions are not exclusive but coordinate with each other [41].

Inhibition of the Toxins: Antitoxin anti-bodies can block the binding of toxins to the receptors and prevent the toxin necessary structural changes for toxicity and form immune complexes that assist toxin example Bezlotoxumab neutralizes the toxin TcdB of clostridium difficile by directly attaching to its two distinct sites E1 and E2 [43].

Inhibition of the Virulence Factors: Anti-bacterial mAbs can target virulence factors on the surface of bacteria to hinder pathogenicity. Both KB001 A and V2L2MD inhibit the type III secretory system on the surface of pseudomonas aeruginosa and prevent the bacteria from injecting toxins into the cytoplasm of host cells by targeting *Pseudomonas aeruginosa* (PcrV) protein [44]. Antibodies mostly produced in mammals provide a useful alternative in the treatment of bacterial infections either directly or indirectly by targeting bacterial surfaces. However, several challenges face in the production of the IgG antibodies in mammals which includes weak immune response of the antigens [45]. The most efficient and economical approach for the production of the antibodies without harm caused to the animals has led to a growing interest in the egg yolk antibodies. IgY [46] antibodies are reported as a potent preventive and therapeutic agent several viruses such as influenza [47] ARotavirus [48] Dengue [49] Zika Ebola and SARS COV2. The use of IgY antibodies against the infectious disease minimize the risk of developing AMR since the antibodies are directed to various antigens of the same microorganism [49], IgY is an alternative for use in human and veterinary health to combat the emergence of resistant bacteria [50]. It is environment friendly and elicits no undesirable side effects, disease resistance or toxin residues. The main advantage of the IgY is it does not disturb the host flora [51].

Phage Therapy: Bacteriophages were first found by Felix d'Herrelle and Frederick Twort over a century ago. Many changes has been since its start. So-called phage therapy was extremely attractive to d'Herrelle and others in the early 20th century as it offered the first believable solution for threatening

bacterial infections. Such infections were common and often serious, and were major factors in determining average human life expectancy, which in 1900 in the United States was 47 years. However, the discovery of antibiotics and their use in the 1940s and beyond proved a more powerful and widely effective antimicrobial solution [52]. Renewed interest in the therapeutic use of phages often mirrors concerns about the emergence of antibiotic resistance and the prospects of a post antibiotic era with antibiotic resistance declared by the World Health Organization to be one of the biggest threats to global health, food security, and development. The rapid growth of resistance to antibiotics is determined by their overuse and misuse, but it is not really a surprise, as the bacterial pathogens respond to the excessive selective pressures placed upon them. The therapeutic use of phages would seem to be among the best of all potential alternatives to respond to this urgent global need [53].

Phage Biology: During a lytic infection cycle, a phage attaches to bacterial receptors, delivers its genetic material, undergoes replication within the cytosol via bacterial machinery, and releases new phage particles by lysing the bacterium. This self-amplifying process underscores the efficiency of phage therapy compared to antibiotics, which lack self-replication capabilities. In compassionate-use scenarios, phages are often used alongside antibiotics, potentially interacting synergistically or additively. While phage resistance can occur, its frequency varies across bacterial species, influenced by factors like receptor variation and other defense mechanisms such as restriction systems or prophage-encoded defenses [54].

Phytochemicals: Phytochemicals are bioactive non-nutrient compounds found in plants, particularly in fruits, vegetables, and grains, known for their potential to reduce the risk of chronic diseases. These compounds provide plants with natural defenses against bacteria, fungi, and pests, and are responsible for the antimicrobial properties observed in plant extracts tested *in-vitro*. Photochemical reactions occur when these molecules absorb light, causing electrons to become excited and move to higher energy states. This excitation can trigger various chemical processes depending on the molecular structure and the wavelength of light. The interest in plants with antimicrobial properties has grown due to rising concerns over multidrug-resistant bacterial strains like methicillin-resistant *Staphylococcus aureus* and Helicobacter pylori. Herbal remedies are increasingly recognized globally, particularly in regions where access to conventional antibiotics is limited or costly. Medicinal plants continue to be investigated for their potential as sources of new antibiotics, with phenolic compounds often highlighted for their antibacterial activity against gram-positive bacteria. Various methods, including agar diffusion and dilution assays, are employed to evaluate the antimicrobial efficacy of plant extracts and essential oils under laboratory conditions, facilitating ongoing research into new therapeutic agents [55].

CONCLUSSION: As AMR continues to emerge and spread beyond all boundaries the effective implementation of various strategies to combat AMR is needed which is a complex problem with diverse contributing factors. It directly or indirectly influences the cost of patient and the community. Several new strategies have been tested to enhance antibiotic efficacy through novel targets and the mechanisms. Addressing this complex issue demands a multifaceted approach, including innovative drug development, anti-virulence, Monoclonal antibodies, Chemoprophylaxis, Antimicrobial peptides, Phage therapy, Phytochemicals and Nano particle. This will definitely aid in overcoming the current antimicrobial resistance.It directly or indirectly impacts the costs incurred by both the patient and the community.

ACKNOWLEDGEMENTS: The authors are thankful to St Pauls Management for their encouragement and support.

Funding Source: This study did not receive any financial fund.

Ethical Approval: None applicable.

CONFLICT OF INTEREST: The authors have no conflicts of interest to declare.

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How to cite this article:
Mandava K, Ramya B, Boddu S, Balaji M, Qadeer MA, Khaanam A and Are A: Addressing the global threat of antimicrobial resistance: emerging approaches, innovations, and rethinking strategies for future control. Int J Pharm Sci & Res 2025; 16(10): 2670-69. doi: 10.13040/IJPSR.0975-8232.16(10).2670-69.