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Modern Approaches to Combat Antimicrobial Resistance: A Review

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ABSTRACT

The world has taken cognizance of the emergence of the threat of antimicrobial-resistant bacteria in a big way and has recognised the limited antimicrobial options before mankind. The ubiquity of bacteria and their role in our lives makes it urgent for us to solve this problem in a multifaceted manner. As the development of novel antimicrobials is few and difficult to come by, we need to manage our present antimicrobial arsenal prudently and also manage antimicrobial-resistant bacterial infections by applying various alternatives available in the scientific field to treat the diseases. An excellent option is to use new and old clinical therapeutic techniques and molecules to control AMR. Different strategies such as the application of bacteriophages alone and in combination with nano-based and liposomal delivery systems, and the usage of molecular adjuvants and probiotics can fight directly and indirectly against AMR bacteria. In addition, biological molecules such as monoclonal antibodies, vaccines, stem cells, and antimicrobials in conjunction with bacteriophages can be game changers in mitigating the emerging antimicrobial resistance pandemic.

Keywords: Antimicrobial resistance; Liposomes; Bacteriophages; Quorum quenchers

1. INTRODUCTION

Nearly 90 years have passed since Alexander Fleming, in 1928 discovered penicillin G from the mould *Penicillium rubens*. This discovery marked the beginning of a new era in medicine and transformed the discipline of health management. Subsequently, novel antibiotics and synthetic antimicrobial derivatives became available, helping to control infectious diseases such as plague[1-2]. However, not even a century has passed since the discovery of antimicrobials, evidence has started pouring in about the loss of effectiveness of antimicrobial drugs against bacterial pathogens. This has led to the World Health Organisation (WHO) declaring an impending 'post-antibiotic era', a time characterised by the emergence of a higher rate of mortality due to innocuous infections, sepsis, and post-operative septicemia and related events[3-4]. Even at present times, the emergence of antimicrobial resistance (AMR) is causing hundreds of thousands of deaths per year due to nosocomial infections alone, as highlighted by economist Jim O'Neill[5]. If AMR continues to rise at the current rate, it is estimated that by 2050, antibiotic-resistant infections will account for over 10 million deaths annually and cost the global economy up to 100 trillion USD[5]. Presently the estimates for death due to AMR bacterial infections in the USA (20,000 per year); France (13,000 in 2012) and worldwide (700,000 annually) are throwing up approximate numbers which although may be contentious for want of empirical data, are nonetheless indicative of a problem which needs urgent social, political and scientific solutions[6].

The bacterial arsenal to fight against antimicrobial drugs is contained in its genetic material comprising chromosomes and plasmids. Resistance to antimicrobials may be inherently present in the chromosomes e.g., mollicutes are intrinsically resistant to β-lactams and glycopeptides drugs that target the cell wall[7]. Innate resistance of *Pseudomonas aeruginosa* mediated by multidrug efflux systems, including MexAB-OprM and MexXY-OprM is well studied[8]. However, the plasmid-mediated acquisition of novel genes by Horizontal Gene Transfer (HGT) drives the evolution of bacterial pathogens towards resistance. *Escherichia coli* is the prime example of the ubiquitous opportunistic pathogen that can accumulate resistance genes via HGT[9,103]. Mechanisms of AMR in bacteria are a theme or combination of themes of protection against the targeted protein (target protection), change in the structure of the targeted protein (target substitution), production of enzymes with change in antimicrobial structure (antimicrobial detoxification), rapid removal of antimicrobial compounds from microbial cells (prevention of intracellular antibiotic accumulation by efflux), and blockage or prevention of antimicrobial uptake (antimicrobial blockade). Such capabilities in bacteria are achieved by the acquisition of selected genetic changes. Such changes occur either in the form of mutations or more frequently,

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by acquisition of extra-chromosomal genetic repertoire of AMR genes by plasmids[10]. Many strategies against antibiotics in bacteria have been reported, such as enzyme inactivation, changing cell permeability, altering target binding sites, increasing antibiotic efflux, and performing complex phenotype changes (e.g., biofilm formation).

Antimicrobials are broadly classified into narrow-spectrum (targeting specific bacterial groups) and broad-spectrum agents (effective against both Gram-positive and Gram-negative bacteria). However, the use of broad-spectrum drugs often promotes the selection of resistance across a wide range of bacteria, not just the targeted pathogens[102]. While antibiotics have been indispensable since their discovery in the early 19th century, microbes have progressively developed mechanisms to evade their effects[11]. Moreover, new antimicrobial discovery is both slow and expensive, making it imperative to explore alternative strategies to address the growing threat of AMR.

2. NOVEL CLINICAL INTERVENTIONS AGAINST AMR BACTERIA

Since the usage of antimicrobials against bacteria is bound to result in the emergence of AMR hence we must understand and tackle this problem from various perspectives. This is emphasised in the Global Action Plan adopted by the World Health Assembly in May 2015. Among the 5 objectives, the following two focus on prevention and control of AMR. One objective focuses on infection prevention and control, whereas another emphasizes sustainable investment in new medicines, diagnostic tools, vaccines, and other interventions[12]. In this review, we take a view of alternatives to antimicrobials or in combination thereof, which are available to us to manage AMR.

The strategies to combat the challenge of controlling AMR bacteria can be multipronged (Table 1). Since AMR bacteria have evolved multiple intrinsic mechanisms of resistance, methods that work indirectly against microbial enzymes promoting resistance, and directly against AMR bacteria are commonly being pursued. Phytochemicals and plant-derived essential oils are prominent examples of the latter category whereas the use of bacteriophages, antimicrobial peptides, probiotics, monoclonals, and vaccine development are direct methods. Efficient delivery of drugs and combination therapy compounds to local infection sites is an emerging strategy that utilises nanoparticles and liposomes.

2.1 Bacteriophages and Phage Therapy

Bacteriophages (phages) are viruses that specifically infect and kill bacteria without harming human or animal cells104. As natural bacterial predators, they exhibit strong bactericidal activity against targeted strains. Most naturally occurring phages are tailed and belong to the families *Myoviridae, Siphoviridae*, and *Podoviridae*, all of which contain double-stranded DNA. Discovered independently by Frederick Twort (1915) and Félix d'Hérelle (1917), phages were first recognised for their therapeutic potential by d'Hérelle, who pioneered phage therapy-a targeted approach to treat bacterial infections through cell lysis, offering a safer alternative to conventional antibiotics.

One of the major advantages of bacteriophages over traditional antibiotics is their high specificity-they target only specific bacterial species or strains. While this narrow host range can limit their spectrum of use, it minimizes collateral damage to the host's normal microbiota. Unlike broad-spectrum antibiotics, phage does not disrupt the gut's microbial balance, thereby avoiding issues like gut dysbiosis or *Clostridium difficile* infection, which can lead to persistent diarrhoea[13]. This selectivity also helps preserve gut-brain axis integrity, reducing the risk of broader physiological disturbances often associated with antibiotic use. Bacteriophages have gained renewed interest as therapeutic agents due to their ability to kill both antibiotic-susceptible and resistant bacteria. Obligate lytic phages, preferred for therapy, destroy bacteria by producing endolysins-enzymes that degrade the bacterial cell wall during the final stage of phage replication. Purified recombinant endolysins have shown potent lytic activity against Gram-positive bacteria even when applied externally.

Phages also possess the ability to penetrate and

Table 1. Approaches for management of antimicrobial resistant bacterial infections

S. No.	Approaches targeting antimicrobial resistant enzymes	Approaches directly targeting antimicrobial resistant bacteria
1.	RNA silencing: Antisense RNA silencing used to study the function of eravacycline heteroresistant candidate genes in *Acinetobacter baumanii*[106]	Bacteriophages, monoclonal antibodies and mesenchymal stromal cells
2.	Crisper Cas system e.g., CRISPR-cas3 mediated degradation of plasmid[110]	Bacteriocins and antimicrobial peptides
3.	Essential Oils e.g., Aureo-Candidum Essential Oil[107], Ocimum essential oil[108], Thymus vulgaris essential oil[109]	Anti-persistor molecules
4.	Small molecules e.g., Peptidomimetics (Acetanilide, α-mangostin against *S. aureus*)[111]	Prebiotics, probiotics, symbiotics
5.	Medicinal plants and phytocompounds	Quorum quenchers

degrade biofilms, complex bacterial communities that are typically resistant to antibiotics[14]. Importantly, temperate phages are excluded from therapy due to their potential to carry harmful virulence genes, such as those encoding toxins (e.g., CTX Φ)[15]. Instead, therapeutic applications focus on carefully selected lytic phages, avoiding those with lysogenic potential. The foundational technology for phage therapy is well-established and continues to advance.

Generally, against pathogenic agents, phage cocktail therapy is more effective than single phage therapy[16-17]. As the name suggests, it is a mixture of lytic phages that lyse different strains of the same bacterial species. The use of phage cocktails is more effective in treatment given the property of phage specificity, and additionally, it minimizes the chance of development of resistance. The cocktail phage therapy of four phages (EW2, AB27, G28, and TB49) supplemented with drinking water was more effective in the prevention of the broiler intestinal *E. coli* colonisation, thus, a barrier in the transmission of the AMR pathogenic strains to the humans from animal source food chain[18]. Phages can be applied as local or systemic therapy. The phage therapy is applicable in both acute infection and chronic infection, and the actual bacterial density at the time of application and the abundance of bacteria may be important criteria. Doses between 10^5 and 10^9 Plaque-Forming Units (PFU) have been used.

Phage therapy has been more commonly practiced in countries like the former USSR, Poland, and Georgia, where interest persisted despite the global shift toward antibiotics. However, several challenges have hindered its widespread adoption. Key among them is the need for high-purity phage preparations, as enrichment often results in bacterial debris or toxins that must be removed. Additionally, precise dosing, timing, and pathogen-specific matching are critical for therapeutic success. Although phage banks are being developed to address the need for ready-to-use phages, custom isolation for specific infections remains a time-consuming process.

2.2 Mesenchymal Stem Cell: Direct and Indirect Applications

In many hospitalisation cases, the patients undergoing surgical implants, or those who are in the process of surgery with indwelling catheters and orthopedic devices, bacterial infections develop which take the form of bacterial biofilms on the surface of such devices. In general, management of such infection is indicated by antimicrobial therapy, however, the emergence of antimicrobial-resistant strains in the hospital environment causes a great deal of difficulty in case management [19,20,105]. Even aggressive antibiotic therapy is not able to resolve chronic biofilm-characterised infections. These are sought to be managed by additional strategies like the use of antibiotic-impregnated implant materials, biological scaffolds, the use of biofilm disrupting agents, and immunotherapy agents like antibodies along with antimicrobials[21].

Previous work has garnered evidence that Mesenchymal Stem Cells (MSC) exhibit direct and indirect antimicrobial properties. The direct antimicrobial effect of MSC has been elucidated by their secretion of antimicrobial peptides, including cathelicidins, lipocalin-2, and beta-defensins. Indirectly, MSCs have also been shown to interact with the host innate immune system to increase antibacterial activity, by increasing phagocytosis and killing properties of monocytes and neutrophils following exposure to MSC-secreted factors. A recent study has evidenced the synergistic action of antibiotics and MSCs to enhance survival in a mouse model of sepsis. Similarly, a synergistic action of MSCs can be tested along with bacteriophages, especially in topical wound healing experiments. In a research work utilising bacteriophage as a therapeutic agent against *C. difficile*, researchers demonstrated that in a system of human colon tumorigenic cell line HT-29, the phage phiCDHS1 killing activity is enhanced compared to killing in liquid culture. It was found that phage can reduce *C. difficile* numbers more effectively in the presence of HT-29 cells than *in vitro*[22].

2.3 Liposomal Delivery System

Liposomes are microscopic lipid vesicles used to enclose hydrophilic as well as lipophilic compounds, to be used as an efficient drug delivery system[23] (Fig. 1). After intravenous injection, liposomes are taken up by the macrophages in the liver and spleen. Investigation of several animal infection models has shown that liposome-entrapped anti-infectious drugs are active against infections caused by intracellular bacteria, parasites, and viruses like the Rift Valley fever virus. Liposomes of different lipid compositions, structures, and sizes were used for the intravenous administration of anti-infectious drugs without inducing toxicity in the tested animals. Clinical experience was obtained with two different liposomal preparations of amphotericin B in the use of systemic fungal diseases in cancer patients; these preparations were shown to be effective and very well-tolerated[24-25]. Liposome is also used in conjunction with phages e.g., by phage encapsulation in liposomes, especially for gastrointestinal infections, as it can help increase the retention time of phage in the host with better therapeutic efficacy. Phage liposomal encapsulation has also been found to increase the length of systemic circulation of phage. The encapsulated phage has been found to amplify and persist longer in lung samples[26]. Liposomal-delivered phage treatment has also been tested for local wound infections by topical application.

2.4 Monoclonal Antibodies

To combat antimicrobial-resistant bacteria, a novel method of AMR treatment is the development of therapeutic monoclonal antibodies (Mab) which initiate an immune response against pathogens without perturbing the normal functional microbiome[27]. Although therapeutic Mab was being used specifically to treat many infections, they

had many disadvantages linked with Mab administration, dosage, production, and cost. A new method developed to offset these disadvantages is DNA-delivered mAbs or DMAbs. DNA-delivered Mabs are DNA vectors that encode for a fully functional mAb. The vector is injected directly via electroporation into the skeletal muscle. At this location, the vector gets expressed, transcribed, translated, and secreted into the circulatory system. The mAb then acts just the same as another IgG molecule. Researchers at Wistar Institute have utilised this strategy to treat mice infected with AMR *P. aeruginosa*. They injected 2 different DMAbs into infected mice which encoded 2 different mAbs capable of treating the *Pseudomonas* spp. infection. DMAbs can be an economical and feasible choice for AMR treatment[28]. Bacteriophages have been utilised to inhibit cross-reactive non-salmonellae bacteria in the process of detection of food-borne infection by monoclonal antibody-based immuno-chromatography[29]. Bacteriophage lytic enzymes and Mabs (raxibacumab, cAb29) have been tested against the dreaded bioterrorism agent *Bacillus anthracis* as potentially novel treatment options[30, 31].

2.5 Vaccines

Vaccines have been a tool used for a long time to combat various infectious diseases in humans and animals, so their application as preventative methods for the control of AMR pathogens needs to be taken in earnest[32]. The main argument which goes in its favour is that vaccines can prevent infections caused by AMR pathogens. Secondly, by preventing disease in a population, the amount of antimicrobial usage can be reduced. Bacterial pathogens like *Mycobacterium tuberculosis, Salmonella* Typhi, *Klebsiella pneumoniae, P. aeruginosa, Staphylococcus aureus*, pathogenic *E. coli*, and *C. difficile* are major AMR pathogens, against which vaccine development is under track [33]. Similarly, veterinary pathogens like *Pasteurella multocida, Mannhemia hemolytica, S. aureus, Streptococcus agalactiae, Salmonella* spp., Entero Toxigenic *E. coli* (ETEC) etc. can be targeted for the development of better vaccines. Bacteriophages are not able to replicate in eukaryotic cells. Recent work has also demonstrated the utilisation of phage particles to deliver vaccines in the form of immunogenic peptides attached to modified bacteriophage coat proteins or as delivery vehicles for DNA vaccines, by incorporating a eukaryotic promoter-driven vaccine gene within their genome[34,35].

2.6 Potentiation of Antimicrobial Activity by Combination Therapy with Non-Antibiotic Adjuvants

Among the various strategies adopted by bacteria to become resistant to antimicrobials, certain strategies make use of prevention of uptake of antimicrobials inside the cell by decreasing the permeability of Gram-negative bacteria cell membrane by mutations induced changes in porin proteins, or loss of porins 36. The expression of OmpF and OmpC in *E. coli* and OmpK[35] and OmpK[36] in *K. pneumoniae* has been detected to be reduced in the carbapenem-resistant strains[37,38]. Bacteria remodel the outer membrane to escape the effect of antimicrobials. Combination therapy can counter this with certain chemical compounds interfering in bacterial outer membrane remodeling [39]. Compounds such as mitotane, an anti-cancerous drug, have been used against penmen-resistant *Pseudomonas* spp., *Acinetobacter* spp., and *K. penumoniae*[40]. Another antibiotic adjuvant is SPR471, which increases the bacterial outer membrane permeability thus allowing entry of antibiotic into the cells41. In addition to perturbation in cell-membrane permeability, bacteria use efflux pumps to remove antimicrobials and disinfectants[42,43]. A combination therapy involving compounds that can inhibit efflux pumps against resistant Gram-negative bacteria has been described. It has been observed that under stressful conditions such as heavy

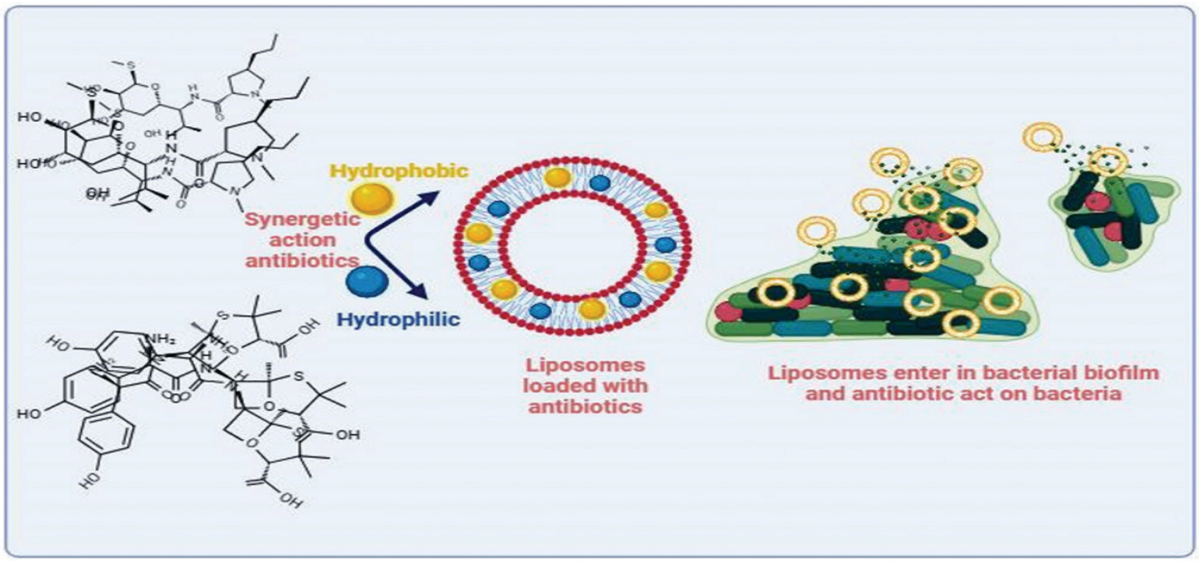

Figure 1. Liposomes as delivery system for antimicrobial agents and phages.

metals in soil; plants produce secondary metabolites[44]. Secondary metabolites such as phenols, terpenes, alkaloids, saponins, lipids, and carbohydrates can be used as Efflux Pump Inhibitors (EPI)[45]. The main mechanism of action is competitive inhibition, as these compounds become the substrate for efflux pumps instead of antimicrobials. Phenylalanyl arginyl β-napthylamide (PAβN) has been used as an EPI for *P. aeruginosa*. Curcumin from *Curcuma longa* has been found to inhibit efflux pumps in *Pseudomonas* spp.[46]. Efflux pump inhibitors have also been isolated from strains belonging to *Streptomyces* spp. Compounds designated EA-371α and EA-371δ have been identified as specific and potent EPIs of *P. aeruginos*[47-48].

2.7 Phytocompounds

Plant diversity encompasses a huge gamut of pharmacologically active secondary metabolites. They are increasingly being investigated as novel potential antimicrobials owing to their natural origin, diversity, eco-friendliness, and their comparative resistance to the development of antimicrobial resistance. The combined activities of these secondary products usually provide more potentiated benefits. These phyto-compounds target bacterial mechanisms such as intercellular communication, and biofilm disruption in addition to inactivating various enzymes, adhesins, and proteins among others. A study performed using extracts from fruits, herbs, and spices, at sub-MIC titers showed inhibition of Quorum Sensing (QS) by altering the autoinducer's synthesis as well as interfering with its activity[49]. The study further indicated that these dietary phytochemical extracts also inhibited the swarming activity of pathogenic bacteria, an ability also conferred by the QS mechanism. Similarly, the anti-biofilm potential of carvacrol and thymol, extracted from oregano and thyme oils, against *Salmonella* Typhimurium and *S.* Enteritidis on polypropylene, significantly reduced the biofilm formation[50]. The essential oils from *Origanum heracleoticum, O. vulgare, Thymus vulgaris,* and *T. serpyllum* proved to be proactive by inhibiting the biofilm formation by dissolving the mature preformed 48 h. biofilm in a dose-dependent manner[51-52]. The isolated novel phytochemicals can be used as core elements for further designing synthetic compounds having enhanced therapeutic effects. Still, several challenges regarding the intensive use of phytochemicals as an alternative to antimicrobials need to be overcome, such as the development of effective extraction and purification methods, reduction in production costs, and determination of efficacy, safety, and dosage which need to be overcome in due time[53].

2.8 Quorum Quenchers or Quorum Sensing Inhibition/ Impedance

Quorum Sensing (QS) is a cell-cell communication system employed by bacterial pathogens to regulate the expression of certain virulence-associated genes as a function of cell density[54]. The impedance of QS can be a novel antimicrobial strategy. It can decrease the pathogenicity of bacteria instead of inhibiting growth, rendering it less prone to resistance development pressure[55]. The QS is mediated by acyl-homoserine lactones (auto-inducers), receptors, and downstream cascade proteins, practically any component of which can be targeted for inhibition of signals (Fig. 2). The AHL system, in turn, is regulated by LuxI and LuxR protein families which ultimately regulate the expression of QS target genes[56]. For example, synthetic furanone compounds were reported to interfere with quorum-sensing in mice lungs with *P. aeruginosa* infection, while reducing the severity of the symptoms and prolonging survival [57]. This strategy has also been explored in veterinary medicine, food processing, food safety, aquaculture, environmental protection, and agriculture[58]. Three approaches can be taken for quorum quenching inhibition of auto-inducer production, enzymatic degradation of auto-inducer, or inhibition of ligand-receptor interaction and their downstream cascade[59,60]. Moreover, the interference with QS can also be employed

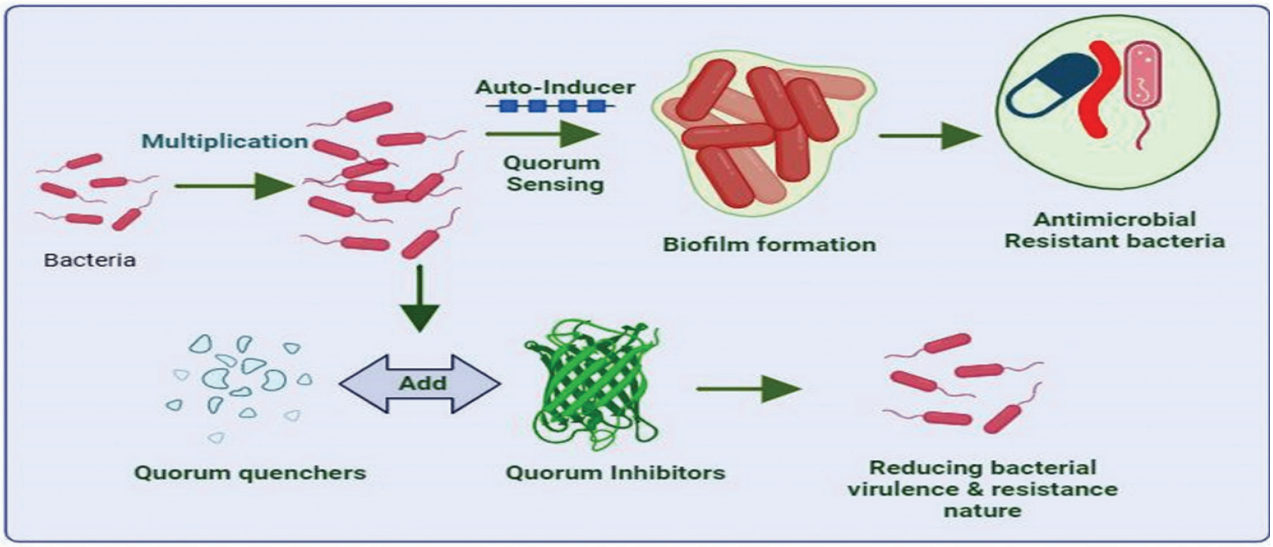

Figure 2. Quorum sensing in bacteria and its interference by quenchers and inhibitors.

to control directly or indirectly the complex resistance mechanisms associated with bacterial resistance such as biofilm formation, bacterial secretion systems, and efflux pumps which impart multidrug resistance to the bacteria[61]. Additionally, the bacterial AHLs (acyl-homoserine lactones) molecules can cause apoptosis in mammalian cells and modulate the activity of NF-κB, which is critical for innate immunity, indicating their possible control by antibodies[62]. However, AHL signal molecules themselves cannot be directly used as immunogens due to their small size and unstable nature.

2.9 Nanoparticles

The ability of certain pathogens to evade phagolysosomal digestion inside the macrophages and intracellular survival has increased the concerns put forward by antimicrobial resistance. Many factors can be underlying causes responsible for the inefficiency of the available drugs against such infections[63]. There have been several reports regarding the potential of NPs as delivery vehicles for antimicrobial agents in several fields such as medical science, veterinary sciences, food science, etc. The nanometer size and high surface-to-volume ratio are the fundamental factors attributing bactericidal effectiveness to these metal nanoparticles[64-65] which allows them to disrupt the integrity of bacterial membranes via electrostatic interactions. Also, being nonspecific to any surface receptor, they reduce the chances of developing resistance against them. They are known to induce oxidative stress by producing reactive oxygen elements. They also cause protein and enzyme instability, inhibit the efflux pump activity, alter gene expression, and quicken the host immunity[66]. The antimicrobial application of copper oxide (CuO) nanoparticles was documented against methicillin-resistant *S. aureus* (MRSA) and *E. coli*[64]. Also, this activity was found to be increased when supplemented with silver nanoparticles. Similarly, selenium nanoparticles were found to be effectively bactericidal against drug-resistant *M. tuberculosis* (Mtb) showing drug-stimulated and phagolysosomal destruction of Mtb when used synergistically with Ison@Man-Se NPs, which was found to be involved in promoting lysosomal fusion of Mtb and hence isoniazid mediated lysis[67]. Anjum and coworkers[68] demonstrated the efficacy of antibiofilm formulation using anacardic acid (Ana) encapsulated solid lipid nanoparticles (SLNs), coated with chitosan and DNase (Ana-SLNs-CH-DNase) against *S. aureus*. Mahmoud and coworkers reported antibacterial and antibiofilm efficacy against *S. aureus, P. aeruginosa,* and *Streptococcus pneumoniae* for silver nanoparticles alone and enhanced activity when used in combination with vancomycin[69].

2.10 Bacteriocins

Bacteriocins are antimicrobial peptides or proteins, ribosomally synthesised and intended to inhibit the growth of or kill closely related bacteria in a competitive environment after they are released extracellularly[70]. They are often confused with antibiotics, but they can be differentiated from the latter based on the site of synthesis. Bacteriocins are ribosomally synthesised whereas antibiotics are secondary metabolites. Also, the mode of action, and mechanism of tolerance in the target cell and the activity range are significantly different[71].

Being implicated in microbial food safety and clinical applications primarily, they have been isolated from both Gram-negative and Gram-positive bacteria, the most crucially studied examples being Lactic acid bacteria and *E. coli*, respectively. The categorisation of bacteriocins has been revised several times after the initial proposal by Klaenhammer[72]. The most recently proposed classification scheme divides the bacteriocins into two groups: Class I–heat stable, a product of ribosomal synthesis and post-translational modification, also called lantibiotics, and Class-II- heat stable, unmodified smaller-sized (<10 kDa) peptides and Class-III thermo-labile, large sized (> 10kDa) peptides[73]. The bacteriocins commonly studied include those produced by Lactic acid bacteria (Gram-positive), namely- nisin (*Lactococcus lactis*), sacacin (*L. sakei*), pediocin (*Pediococcus acidilactici*), lactocin (*Lactobacillus sakei*), acidocin (*L. acidophilus*). Those produced by Gram-negative bacteria are colicins and microcins (*E. coli*). Bacteriocins target several essential functions such as pore formation, inhibition of cell wall synthesis or the critical steps of central dogma. Bacteriocins deploy various interaction modes with the target such as docking at the surface using the membrane lipids or proteins (as transporters) or having electrostatic interactions with the target surface. They have wider applications as novel antibiotics as they are specific against several clinically important bacteria including Multi-Drug Resistant (MDR) bacteria, show less cytotoxicity, and can act in broad and narrow range, subject to bioengineering or gene manipulation[71]. Additionally, bacteriocin-based products are available commercially for treatment as veterinary medicines and food additives among others. For instance, nisin, a broad range class I lantibiotic is approved by the WHO, Food Development Authority (FDA) in the USA and the European Food Safety Authority (EFSA)[74] and in use since the 1950s. Similarly, nisin-based products such as Wipe Out® dairy wipes (Immucell, Portland, ME) against mastitis caused by *S. aureus, Streptococcus uberis,* and *Streptococcus dysgalactiae*, Mast Out® (Immucell) and Lacticin 3147 produced by *Lactococcus lactis* DPC3147 have been successfully tested against mastitis-causing pathogens[75]. Therefore, the scope of bacteriocins can be explored further as an alternative to antibiotics.

2.11 Antimicrobial Peptides (AMPs)

Antimicrobial peptides are a widespread group of amphipathic bioactive short proteins that act as non-specific innate immune system components and natural antibiotics and are found ubiquitously, ranging from unicellular to multicellular organisms. They possess a broad spectrum of targets including bacteria, viruses, fungi, and

tumorigenic cells. They also exhibit immunomodulatory ability[76]. The bactericidal effect is exerted by either cell-membrane disruption or various inhibitory effects such as interference with other cell components or biosynthesis of vital macromolecules of host cell[76]. Three modes of action have been defined. In the barrel-stave mechanism, AMPs form transmembrane pores by intercalating into the membrane. In the toroidal-pore mechanism, AMPs form membrane-spanning pores along with integrated lipids. In the carpet mechanism, peptides spread densely on the surface of the membrane in a carpet-like way, thereby breaking down the layer without forming membrane-spanning pores[77]. AMPs are usually cationic, facilitating their interaction with bacterial membranes; however, they comprise a diverse class of structures and sequences. In a study, peptide MSI-78 and OTD-244 were combined with colistin separately and it was found that the colistin MIC decreased to 4-fold for 75 % of the colistin-resistant mcr-1 (mobilize colistin resistance) bacteria, with no effect on the RBC haemolysis[78]. Various non-ribosomally synthesised AMPs (mainly produced by bacteria) such as gramicidin, polymyxin B, bacitracin, nisin, colistin, daptomycin etc., are approved, and in clinical use[79] whereas several AMPs are undergoing clinical trials[80]. Instances of bacteria developing resistance to AMPs are also known[81] but it seems energetically highly unfavourable for the bacteria. Studies are also being done for the antibacterial activities of their structurally modified counterparts such as enhanced bactericidal effects even under unfavorable conditions and narrowed host range[82]. In one such study, Pandit and co-workers[83] designed undecapeptides (AMP21-24) which were salt-tolerant, non-haemolytic and non-toxic, by modification of a peptide P5 (NH2-LRWLRRLCONH2), active against ESKAPE bacterial and fungal strains as well. The study also demonstrated stronger AMP-membrane interaction and intracellular localisation of the AMPs, indicating their secondary mode of action. Although AMPs harbor very potent bactericidal ability, various constraints are also observed such as poor stability, toxicity towards eukaryotic cells, and appropriate drug administration route [84-85] which need to be reconsidered and focussed to classify them as successful replacements to antibiotics.

2.12 Prebiotics, Probiotics, and Synbiotics

Multidrug-resistant organisms of the enteric microbiome exist as a potential target that can be manipulated to withhold the spread within the community. With the ban of antimicrobial agents as feed additives, there is increased acceptance of products based on probiotics, prebiotics, and synbiotics as natural growth promoters and ways to have a healthy gut. This applies to humans as well as the livestock industry. Probiotics are living bacteria added to foodstuffs. These are aimed at improving health, especially gut microbiome. Probiotics as dietary supplements are proven to help induce healthy gut microbiota composition, modulate the gut nutrient metabolism, solute secretion and absorption, increase luminal bile acid concentrations[86,87,88,] improve intestinal epithelial integrity, and possess mucosal immunomodulatory functions[89]. Published literature has shown promising results for the control of resistant strains by the use of probiotics. For example, lactobacilli and bifidobacteria were found to abolish colonisation of *S. aureus* and MRSA clinical isolates *in vitro* studies, including interference with *S. aureus* biofilm and lipase production[90]. Also, Pipat Piewngam *et al.,* have reported inhibiting growth of *S. aureus* by probiotic *Bacillus* bacteria and showed *Bacillus* lipopeptide, fengycins, to be quencher of quorum sensing-based signalling[91]. A very promising, first-of-its-kind study revealed the eradication of Vancomycin-Resistant Enterococci (VRE) following consumption of *Lactobacillus rhamnosus* GG (LGG) incorporated into yogurt, compared with placebo[92]. In another study, a triple therapy consisting of fermented milk product incorporated with *Lactobacillus casei* DN-111001 strain and antibiotics Omeprazole, Amoxicillin and Clarithromycin (OAC) when administered to *Helicobacter pylori* infected children were found to be successful over the group who received only OAC[93]. Similar attempts were performed against ESBL-producing *Enterobacteriaceae*, however it proved no superior over placebo[94,95].

Prebiotics are non-living, non-digestible food components that are fermented selectively by the gut flora and provide a favourable environment for the gut commensals growth, while in doing so, increasing the gut diversity and health benefits[96,97]. However, they are not as popular as their probiotic counterparts, given the number of factors that need to be controlled while formulating such agents. On the other hand, synbiotics are mixed preparations of probiotics and prebiotics designed to supplement gut health. They are known to lower intestinal pH, which adjusts the intestinal micro-flora and restricts the detrimental bacterial species of the gut, along with augmenting lactate and antibody production when used as additives to animal feed[98]. The synbiotics were also reported to improve gut health thus reducing the antimicrobial usage and hence, the antimicrobial resistance[99]. Therefore, there is a need to optimize the bacterial species and dose to avoid the risks and uncertainties associated with such strategies.

3. CONCLUSION

The emergence of AMR is not a threat but a reality, which is looming large over mankind just like a tsunami after an earthquake. The indiscriminate spread of antimicrobial compounds in nature is the earthquake that has given rise to this imminent tsunami. Therefore, humankind needs to take stock of the situation and employ all their knowledge and techniques to bear upon the AMR pandemic. Given the multifaceted aspect of the AMR problem, research and development efforts need to be coordinated with a multidisciplinary One Health approach to tackle AMR in all sectors. Governments need to appreciate and promote R & D to foster novel approaches to efficiently use what has been left of the antimicrobial arsenal against resistant bacteria. The emergence of AMR has again necessitated

the need to look towards phages. The discoverer of phages, D'Herelle pioneered incorporating phages in veterinary applications by using phages against fowl typhoid induced by *Salmonella* Gallinarum in chickens[100]. It is therefore very important that the traditional rivalry of phage and bacteria be exploited in manifold ways in the prevention and control of bacterial infections[101]. There is a growing need to broaden the scope of bacteriophage research, including the systematic isolation and characterisation of phages targeting a wide range of clinically relevant bacteria. Beyond phages, a comprehensive response to AMR must also harness the full potential of alternative compounds such as bacteriocins, antimicrobial peptides, plant-derived bioactives, vaccines, immunotherapies, and probiotics. These can be used independently or synergistically with existing antimicrobial agents to improve therapeutic outcomes.

Additionally, several cutting-edge technologies are on the horizon, including RNA interference (RNAi), CRISPR-Cas-based antimicrobial systems, anti-persistor and anti-plasmid therapies, and photodynamic and sonodynamic antimicrobial chemotherapy. While these approaches show promise, they are still in the early stages of development and require rigorous research and clinical validation to ensure their safety, efficacy, and scalability for real-world application.

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